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## IN THE SPIRIT OF SERVICE \*

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"Where there is love of the art there also the love of man is"—Hippocrates

As members of the medical profession, we are becoming increasingly conscious that all is not well in our house. Doubts are being implanted in the minds of laymen concerning the efficacy of established practices which organized medicine has set up for the protection of society. Propaganda for the socialization of medical services is encountered on every hand. The motives for professional objection to even the most fantastic schemes for providing medical care are misunderstood.

There has never been a time when the medical profession has had so much to offer the people as in this year 1939. From research laboratories and the bedside, discoveries of great significance flow in increasing volume. In the fields of biophysics, physiology, biochemistry, chemotherapy, immunology, nutrition, endocrinology and in their spheres of clinical application, we witness the most remarkable scientific advances the world has ever known.

This is the Golden Age of medicine. We grow so accustomed to spectacular pronouncements that our critical faculties have been weakened. The reactions in the laboratories scarcely cease before the products of research are rushed to the bedside. It is said that the proprietary manufacturers, like prowling jackals awaiting the feast, embrace every opportunity to capitalize upon the discoveries. Witness the deluge of vitamin and endocrine products, the host of chemical compounds under many proprietary names, and the other nostrums distributed through the profession or sold directly to the public. These proprietary drugs are sold over the counter in variety drug stores where the dispensing department is well disguised behind an

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It should be understood that any statements or comments made in this address or any opinions given are entirely personal and do not necessarily reflect the consensus of opinion of the membership of the American College of Physicians. It is not implied that the College has taken any action or intends to take any official action for the solution of any of the problems discussed.

array of cosmetics, liquors and lunch counters. Our large department stores are catering to the demand for vitamin products at an annual cost to the feminine consumer which would give her full medical protection. Authority should be granted to proper agencies charged with the enforcement of the Food and Drug Act to restrict high-pressure salesmanship dangerous to the welfare and safety of the public. The investigations of the Council of Pharmacy and Chemistry of the American Medical Association should be given wider publicity.

New methods for diagnosis and treatment should be carefully tested before being given to an expectant profession and through it to the trusting public. Too often the harmful effects of a new procedure or a new drug are not easily discernible. The producer (the research worker) has a great responsibility. There is no way for the distributor (the doctor) to judge the worth of new methods except by trial and error. In the end it is the consumer (the patient) who pays the bill and runs the risk, and he is usually in no position to know he has been injured or defrauded.

There has never been a time when the public has been so conscious of the current advances in science. People read of the modern miracles of medicine and are prepared to expect any pronouncement in its name. Since they are unable to discriminate, pseudo-science and cultism flourish to an unparalleled degree in this most enlightened scientific age.

The public are interested in better medical care. We are faced with an increasing demand for a more equable distribution of medical services. Our country has been almost the last to meet this issue. It must be faced wisely for the benefit of all the people and *in such ways that the quality of services shall not be impaired*. It should be apparent to anyone who attended the Washington Health Conference last July that over half the people of our country are demanding the benefits that they believe could be obtained by a more even distribution of these services. Organized medicine has been outspoken in its opposition to some of the proposals advanced for a reorganization of medical practice, because its leaders believe that these proposals if adopted will result in inferior rather than improved service. Other professional groups contributing to the care of the sick apparently agree that some changes are urgently needed, and many reputable members of the medical profession sincerely believe that the proposals made in Washington offer a basis for solution. There has been much criticism of the methods used in the preliminary survey of existing conditions, but no more surveys are needed to show that the low-income groups have more sickness and higher death-rates than those in the higher income group. In recent months many of the objections raised by organized medicine have been withdrawn, leaving only the subject of compulsory health insurance for further study and discussion. Anyone who heard the recent demands in Washington must be impressed by the sincerity of the appeal for better health. Never has there been so great and important an appeal to the professional groups contributing to the care of the sick. There are some who hold that the

appeal on the part of some of the groups was ingenuous. Among the representatives of workers with low incomes were some who held the extreme view that all services to the sick should be free and based upon general taxation. It was evident, however, that most of the groups represented expected to contribute toward the cost of services according to their ability to pay, with such assistance by employers and by the public through taxation as would be required to insure the highest quality of medical service.

It is the prevailing opinion that only the rich and the poor secure the best or even satisfactory medical care and that the groups of people with moderate or low incomes are unable to secure proper treatment. This is true within certain limits. The very poor are able to secure excellent care in centers where well established endowed or tax-supported hospitals and ambulatory clinics are provided. Most or all of the cost of services to these people is borne now by the public in one way or another. In private practice this group is cared for by physicians without thought of compensation. The personal services are rendered in a spirit of charity. It is obvious that practitioners cannot afford to pay for the necessary expensive diagnostic and therapeutic services which may be required. Doctors take great pride in their charitable acts, but when a large proportion of their time and substance is donated, the economic burden is greater than they can bear. In those places where free clinics and free hospital facilities are not available, complete medical care cannot be provided. The doctor cannot carry the entire load and survive. The contributions made by the medical profession in these years of depression are enormous and have been estimated by our distinguished president of the American Medical Association, Dr. Irvin Abell, at a million dollars a day. This is probably a conservative estimate. Doctors, led by charitable motives, are being subjected to an economic pressure which is bringing the income of many of them below the level of respectability and often below the level of mere subsistence. Among those contributing to the care of the needy sick, they alone are giving freely of their services while all others are paid.

How does it fare with the large middle group? People with low or moderate incomes are unable to pay for full medical services. They seldom see a doctor unless symptoms are severe, and often it is too late to secure the best result. They receive little or no preventive treatment. They can neither save for catastrophic illness nor contribute to a fund for proper distribution of medical services.

It is generally stated that the well-to-do have the best of care. The rapidly vanishing group of the wealthy members of society can afford to secure the best medical services. However, it does not follow that they get it. The chief obstacle lies in the tendency to over-specialization in our larger centers. Many well-to-do families have no one general physician who acts as the family advisor and who arranges for the services of specialists when needed. They often go directly to specialists; each member of the family makes his or her own diagnosis and takes the complaining organ or

part to the chosen specialist. Like doctors, they sometimes make mistakes! Often there is reference from one specialist to another without anyone supervising the general care. We could use the British system to advantage wherein the general practitioner is the health supervisor of the patient. The lack of general practitioners in some of our group clinics encourages people to be their own diagnosticians.

We hear much discussion of faulty distribution of medical services. There can be no doubt that there are great gaps in our methods of distribution. The economic situation affects the public and the profession alike. There can be no doubt that sickness, disability, and untimely death increase with poverty and the ability of the agencies to render adequate service depends largely upon some source of funds to pay for it. We should not be satisfied with a remarkable general record of good health in this country when we know that still further improvements could be made if we applied the knowledge and methods now available for control of disease. There are large numbers of our people who have no preventive treatment and no curative treatment except in great emergencies. It would require many millions of dollars to provide these services, but the amount would be small in comparison with the enormous sums now being spent to care for those suffering from diseases that could have been prevented or to conserve the resources lost through untimely death. It should be stated and emphasized that we do not yet know the causes of all diseases and that we still do not have the means to prevent all diseases. And even if we had all the means and they were offered to the public on any reasonable basis, there is no certainty that the people would avail themselves of these services. The opposition to smallpox vaccination often encountered offers an object-lesson in this regard. Some people are against one thing, some against another, and some are contrary enough to be against everything.

Anyone who takes the trouble to inquire or just to listen will soon learn that the medical profession is not generally held in high esteem by the public. The reasons for this growing antagonism are not far to seek. The quacks and faddists who attempt to enter the practice of medicine through the back door have coined the catch-term of "medical trust" for all who oppose quackery in any form. Even in some high places, organized medicine is charged with monopolistic trends. Attacks are made on the medical profession in the courts when freedom to experiment with new and questionable methods of rendering service to the sick is opposed by representatives of organized medicine.

The doctor is blamed for the high cost of sickness. He bears the brunt of criticism which is largely the result of changing economic factors. Most of the increased cost of sickness is due to the use of expensive procedures, the cost of hospitalization, the need for expensive drugs, and nursing and other services. An analysis of the costs of medical care shows that the doctor is not overpaid. As a matter of fact, he is the last to be paid. Often his bill has to be reduced in amount or even cancelled because the patient is not able to meet it.

There is widespread criticism of large professional fees required of those with higher incomes. It is probable that certain specialists make charges beyond reason for services rendered. While this is more prevalent in the surgical specialties, it is not limited to them. There are too many who capitalize on some technical procedure in which they have achieved skill. The specialist whose field of vision is confined to what he sees through a system of lenses inserted into some aperture of the body and who ignores the patient as a biological unit is a menace not only to the patient and the public but also to the standing of his profession. Sir Frederick Gowland Hopkins referred to these practices as "the mastery of technique over reason."

One reads and hears a great deal, stated in jest, about the popularity of operations. In times of distress, patients crave action and readily submit to operations recommended by those whom they trust. There can scarcely be any doubt that in this country too many operations are performed. Many specialists, highly skilled in their technics, are so incompletely trained in general medicine that they do not know the limitations of their method or the comparative value of other methods. Many unwise surgical procedures are performed by poorly trained graduates who rush from our schools into practice anxious for practical experience. It cannot be said that the profit-motive generally determines the method of treatment, but in some instances it would appear that sound judgment had wavered because of this motive. Much of the criticism by the public has been directed toward self-appointed surgeons who favor mechanistic treatment of most diseases. Why are many operative conditions more common among the rich than among the poor? Why do we have waves of popularity for operations for many diseases in which the operative mortality is higher than the natural death-rate? Sometimes when we see a neurotic patient, with many scars of previous operations, we wish that her doctors had been wiser or that they had been denied the great benefits that anesthetics and aseptic methods had brought to mankind. There is an increasing tendency among doctors to recommend exploratory operations on the assumption that the operation is relatively safe and the dangers of waiting for developments are great. Knowing the psychic and physical risks the patient takes under the circumstances, we should take a firm stand against this practice.

One of the great evils of medical practice in this country is "fee splitting" in one form or another. Untouched by codes of ethics and the influence of our great national organizations, there are sections of the country where a division of fees is almost the rule rather than the exception. It is a common practice for unethical doctors to deliver their patients wholesale to specialists for rebates which are frequently half or more than half of the fees. How can the interests of the patient be served under these circumstances? What is to be done about it? At the New Orleans meeting of the American Medical Association in 1903 and at subsequent meetings, an attempt was made to stamp out this practice. Discussions on this subject led to an exposure of the custom, which was a by-product of the lush period

of proprietary medical schools. Out of this situation arose the American College of Surgeons, founded in 1913 largely in an attempt to control this practice. Since that time, efforts have been made to curb the evil, but it flourishes largely outside the membership of national societies of specialists and probably chiefly among practitioners who are not members of the great body of organized medicine. The evil could be corrected by recognizing the services of the practitioner who discovers the condition requiring special treatment and compensating him adequately. But the patient must be made a party to the transaction. There can be no doubt that the people are becoming aware of the custom of fee-splitting, and they don't like it. During the past month two patients from widely separated places asked to be referred to ethical surgeons if special treatment were required. We should find some means to correct this situation for the honor of medicine and the welfare of the public. Let us join with all professional agencies to stamp it out. If it requires the coöperation of the public to reach those not bound by ethical standards or loyalty to any national society, then let us go directly to the people.

It should be recognized also that groups and clinics are generally organized financially upon the basis of a division of fees. Salaries for the members of the group are equalized, with some adjustment for experience or ability. The entrance of the business manager into the group has brought new problems. The psychological values of salesmanship are not lost on him. Diagnostic services are often rendered at low fees, and frequently below cost; and a profitable income is derived from surgical fees. This inculcates into the minds of the public a false set of values. It creates competitive problems for the practitioners and internists outside such groups. In large sections of the country, individual or private practice suffers. When services including diagnostic procedures (the staples) are offered at less than cost in order to attract patients who, when requiring the care of specialists, pay luxury prices for it, we are faced with a critical situation. When the practice of medicine thus enters the citadel of trade and commerce, it should be controlled by the practices and rules of trade. The regulations of the Federal Trade Commission govern the sale of commodities. A tradesman cannot lure the customer into his shop through bargain sales of "loss leaders" to reap a large profit from the incidental sale of a luxury. It should not be allowed in medical practice which, through the trends just mentioned, is being conducted on a business basis. What has been said of group practice applies equally to surgeons who make no charges or only a token-charge for diagnostic services. Such methods are too similar to those of quacks and advertising "specialists" who conduct a "come-on game" through the lure of free examinations.

Fee-splitting is not limited to doctors. Opticians and druggists sometimes divide fees or give commission to doctors, some doctors give commissions to druggists and runners and some chase ambulances. Fortunately, these exert a minor influence in the conduct of medical practice.

A few in the medical profession feel that they have a proprietary interest in patients. How much of this is motivated by the commercial interests mentioned above is difficult to determine. In small communities, this interest tends to cause unfriendly feelings among doctors, arousing jealousies and sometimes hostility.

If fees were equalized, as they may be under a scheme of social medicine, many of the defects of medical practice may be corrected. Some of those who oppose any change from the former status may do so because they know independence of action gives them license to carry on sharp methods in the matter of fee-splitting.

Another factor tending to divorce the public from reliance on doctors is the flood of proprietary medicines put up in attractive and palatable form. They are offered for sale over the counter and heralded from the air and by the printed word. Self-diagnosis and self-treatment convince people that they have no need for doctors when for a small sum they can get temporary relief for imaginary acid indigestion, constipation, a headache, a pain or a threatening cold. The obliging and less scrupulous druggist can and often does profit from this large class of people who never see the doctor until such measures fail or until it is too late for the doctor to be of real service.

Some of the major problems in medical practice are being studied intensively and progress is being made. It should be obvious that better preventive and curative service could be rendered if the best skill and facilities of the medical and allied professions could be made more generally available. This may require the establishment of groups of practitioners in easily accessible centers with hospital and laboratory facilities of the highest standards operated in close coöperation with public health officials. Doctors, dentists and other professional workers will redistribute themselves if attractive opportunities are offered. Some means must be found to pay for minimum or adequate standards of service. The public now pays for most of the free care given in the several states and should be prepared to meet a part of the costs for the borderline and low income groups. The sharing of risks through group insurance is well understood in this country, and it is through this method that the costs may be equalized. Voluntary health insurance may be preferable for those who can meet their share of the cost in the operation of the plan, but how can we expect those with marginal incomes or no income to contribute? One cannot volunteer to contribute to any scheme when he has nothing to divide. If his income does not provide the basic needs for food and shelter, these and health services must be provided under any social system. Industry may share in the expense for care of the wage-earner but not directly for his family or those not employed. The governing units now make a variable contribution to the poor and needy largely for emergency or custodial care but do little for the borderline group. It would seem to be logical that a plan of compulsory health insurance for all below a certain level of income would be desirable, with contributions by both workers and their employers. Supplementary con-

tributions should be made by counties and states with subsidies by the federal government, adjustable in amounts from each, to bring a total which will insure complete coverage for all services. The chief and to many the unsurmountable objection is the element of politics which would introduce a third party for regulation and control hazardous to the interests both of patient and physician. Such a situation already exists with respect to the workmen's compensation laws, and this is officially approved by spokesmen for organized medicine. It is to be understood that there are abuses under the operation of present industrial accident laws, although the lot of the worker has improved greatly under their provisions. The care of patients under the regulations of the Agricultural Adjustment Act is accepted in many sections of the country, and one doesn't hear of doctors refusing to accept fees for their services. In our municipal and county hospitals, local governmental service of the highest type is rendered by doctors, usually without compensation. Many doctors and others in the professional groups now on fixed salaries are rendering distinguished service. If we are motivated by a real desire for service, the profit motive should not determine the quality of our contributions. Most of us wish we never knew what fees a patient could or would pay for our services. The great contribution of groups and large clinics, private and public, is the submergence of personal aggrandizement and gain to the welfare of the patient and the group. It should be possible to select professional censors in the several states to work with representatives of the other interested parties, including business managers, economists and the public, serving for long terms and not subject to shifting political winds. The patient-doctor relationship must and under this plan could be preserved. It is a favorable sign to see some of the leaders of the profession willing to coöperate for the interests of the public as well as those of the profession. As physicians, we should insist upon control of professional services to the end that they should be of the highest quality. We are not economists or business men, nor are we very good politicians. It is too late to play politics in this matter. Too much of our time and energy has been spent already in trying to hold back or sidetrack a social tidal wave which has shaken our edifice from its foundations. We may now prepare to swim for our lives. We should ask for surf-boards and strong leaders who can steer them and take us safely to shore.

It cannot be assumed that doctors are faultless when they participate in any general plan for medical service. In some of the schemes adopted so far, it is found that a few unscrupulous doctors can find ways to increase income by performing unnecessary operations, by dressing a sore finger an unreasonable number of times or by visiting a patient with hay-fever three times a day for a month—to give but a few examples. It will be found necessary to supervise the conduct of practice to prevent the few from discrediting the work of the rest. We should put our own house in order. As one tidies up for company, we should prepare for the sociologists, economists and business managers who are invading the temple of Hygeia. It will not

do to sweep the crumbs of unethical conduct or shady practices under the rug of loyalty to members of the profession—right or wrong. It only weakens our position with the people whom we serve.

The foregoing remarks are not made to discredit our profession which, through the centuries, has attracted men with the greatest devotion and sacrifice for their fellow-men. Our weaknesses must be recognized. Self-analysis in the face of external criticism may help us to regain public support for our profession which by its nature should be most intimately associated with the lives and health of our people.

How can the American College of Physicians best serve the profession and through them the public? It can exert a great influence on American medicine by maintaining the highest quality of professional services totally free from unethical practices; it can aid in promoting the highest standards of medical education and research; and it can encourage and support continuous post-graduate education. There has never been a time when there has been so much interest in post-graduate education. The annual crop of graduates from our medical schools is increasing both in number and quality. Students are selected with great care, and their training is designed to enrich medicine through the contributions from the fundamental sciences. The thousands of young doctors leaving our schools each year are building fires behind us. These youngsters will soon overtake us, and if we cannot keep up we must get out of the way to let them go by. Perhaps this competition has spurred us to look to our laurels. There are, however, still many remote places and some not so remote where the light of improvement does not yet shine. With your permission, I should like to read some verses written by my wife with my prompting which depict the scene in many doctors' offices. These verses are entitled "The Grad from Timbuctoo" and are written after the manner of Eugene Field's "Little Boy Blue."

*The Grad from Timbuctoo*

The medical texts are covered with dust,  
Neglected and musty they stand;  
And the compound 'scope is red with rust,  
And the journals mold, near at hand!

Time was when the favorite texts were new  
And the 'scope had its daily wear  
'Twas then that the Grad from Timbuctoo  
Left school—and put them there.

"You'll be right here when I've time," he said,  
"And after my rounds are through!" . . .  
Then he hurried off, at last, to bed  
And dreamt that his plans came true.

But as he was dreaming an urgent song  
Woke the Grad from Timbuctoo . . .  
The work came thick, and the money fast,  
He had all that he wished to do.

And always waiting, right close at hand  
While the dust and the rust grew more  
Were texts and journals and microscope  
With the latest of medical lore;

Aye, faithful to Timbuctoo they stood  
Each in its given place,—  
Just waiting the touch of a searching mind,  
And the smile of a willing face;

They wondered as waiting the long years through  
In the dust, without any care  
Why that Grad from Timbuctoo  
Ever got them and put them there!

Then gradually, as the years slipped by,  
The Grad felt his prestige fall,  
And he realized with a sudden pang  
That he hadn't "kept up" at all;

He looked askance at the rust and dust  
And the stack of journals high  
And he knew in his heart he'd never catch up  
No matter how hard he'd try!

\* \* \* \* \*

Are you like the Grad from Timbuctoo  
Who failed in its standards high?  
Will you, as the years go racing along,  
Let the chance to "keep up" slip by?

If so, you'll wonder, while sitting alone  
In the dear old office chair,  
Why other doctors are busy as heck  
And you are just sitting there!

—Dorothy Fish Kerr,  
September, 1938.

Except in a few of our leading medical schools, no well designed plans have been developed to keep the doctor abreast of advances in his field. Many of our medical schools are coöperating with state and county societies in offering refresher courses either at the schools or in centers convenient for large numbers of the profession. Many organizations, such as the American Medical Association, serve their own members and others through their annual meetings. Some, such as the Interstate Postgraduate Medical Association of North America, and several patterned after this organization, bring outstanding teachers and others to large groups of the profession for short periods. In Boston under the leadership of Dr. J. H. Pratt a plan has been instituted to bring general practitioners to the hospital for periods of instruction, and to provide substitutes so that the interests of both patients and doctors will be served. This seems to be a step in the right direction. The doctor at the cross-roads needs stimulation and continued instruction to keep abreast of the rapid changes in medical practice. Since the

practice of medicine is primarily personal and individual, the doctor cannot be absent or unavailable except for brief periods. If a way could be found to keep him up-to-date by a system of substitution or by making instruction available near his home for a few hours a week, much good could be accomplished. Most doctors would be willing to pay for this instruction. In order to insure the highest type of service to the people, it may be wise to require licentiates of the State Medical Examining Boards to show continued proficiency by limiting the years for which a license is granted. This would, of course, presuppose adequate opportunities for instruction and a system of grading through some method of examination or other suitable device.

Continued instruction for the recent graduate is well recognized as a valuable means to proficiency in clinical medicine. Many graduates continue instruction for one or more years in special fields after the intern year, the need for which is taken for granted by most graduates and which is required by many medical schools. The American College of Surgeons is actively engaged in a program of inspection and certification of hospitals qualified to offer graduate training in their special fields. The American College of Physicians is now considering a plan of coöperation with all existing agencies to the end that adequate graduate instruction in the special fields of general medicine shall be provided. The examining boards for the certification of specialists are setting up standards and outlining the content of schedules of instruction that will be acceptable for qualification. This is causing some concern to administrators of hospitals and medical schools, and in many instances is unfair to recent graduates. The American Board of Internal Medicine allows some freedom to those intending to qualify for certification. The stand is well taken that we should not be concerned with the method by which proficiency is gained. The product is what we should examine.

The problem of keeping up after the many hurdles are passed is of great concern to the American College of Physicians. Our annual session offers unusual opportunity to hear what is new and important. Our programs are developed with great care to bring distinguished contributors from all fields of medicine before you. Our special short courses are offered to meet the demands of our members. As we gain in experience we shall be able to utilize more fully the resources of our medical schools where generous coöperation is ours for the asking. Through these means and through the medium of the *ANNALS OF INTERNAL MEDICINE*, some of the interests of our members are being served. When other objectives of the College are defined, it may be taken for granted that they will be based upon a desire to elevate the standards of medical practice, education and research, and through such improvements to serve humanity.

There has been some discussion about educating the public in matters of health. There has never been a time when the people have been so interested in science and medicine. Announcements of discoveries are being made through all the mediums of publicity. The people have no means of dis-

tinguishing the good from the bad, and fraud and deceit thrive in minds accustomed to hearing of modern miracles in these fields. Some decry any effort to pass on the results of experiment and practice to the people, but there can be no valid objection to general education along proper lines. The people need to know how to use the services of doctors and others contributing to the purposes of sound health; how to choose a good doctor; and how to meet emergencies until the doctor comes. It would be of great educational value if the United States Public Health Service would undertake to put into the hands of every family a book or pamphlet on matters of health. Frequent revisions could keep the contents up to date. The editorial board should include authorities in all fields of medicine and other professional groups, but they should remain anonymous. In the several states a list of qualified general practitioners and specialists could be included for guidance of the people. The contents should include information on general health and how to maintain it. Prenatal and postnatal care of the mother and child should be discussed. For the life emergencies, there should be instruction on measures to take until the doctor comes, and how to coöperate with him and others afterward. Hazards of life and health which can be avoided should be made known to the people. If properly presented, this instruction would reduce the use of nostrums and cure-all methods of treatment which are now a great source of profit to unscrupulous promoters, and may be injurious or result in loss of precious time.

This is but a brief discussion of the many problems confronting us as a profession. The great majority of our colleagues are inspired primarily with a desire for service. Medicine must always remain the keystone in the arch of service, supported by *les voussoirs* of public health and preventive medicine, dentistry, nursing, social service, technical service and hospital management, and based upon the piers of research and education. Through this arch the public shall pass to a fuller realization of the value of scientific achievement and come to have a better appreciation of the motives which inspire us all.

The American College of Physicians welcomes to its fellowship tonight many who have achieved the merit of high professional attainment. It is our firm conviction that during the period of changing ideologies in medical practice, you will help us to hold aloft the torch of service. May we all cling to the motive that first led us to study medicine: the desire to be of some service to suffering humanity! And as we go our rounds, may we always repeat our salutation when we became doctors of medicine:

We who are about to serve salute you.

**Servimus te Salutamus.**

## CHRONIC IDIOPATHIC HYPOPARATHYROIDISM; REPORT OF SIX CASES WITH AU- TOPSY FINDINGS IN ONE \*

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"CHRONIC idiopathic hypoparathyroidism" is a disease identical with postoperative hypoparathyroidism except that the agent which has interfered with the parathyroid function has not been established. Certain criteria must be fulfilled before the diagnosis can be made. The serum calcium level should be low, but a more important point is that the serum inorganic phosphorus level should be increased.<sup>1, 2, 3</sup> Renal insufficiency, however, should be ruled out as a cause of the hyperphosphatemia. The bones should be normal by roentgenograms in order to rule out rickets or osteomalacia as the cause of the hypocalcemia. The teeth, however, as might be expected from the work of Erdheim,<sup>4</sup> may show characteristic developmental defects if the disease started before dental maturity.<sup>5</sup> The signs and symptoms of tetany should of course be present, but they serve merely to call attention to the tetany and do not help in determining its type. Cataracts and trophic changes of the nails may be present but are not specific for idiopathic hypoparathyroidism.

Tetany is encountered in a number of diseases in no way related to underfunction of the parathyroid glands. These diseases may be divided into two groups: (1) those with a low serum calcium level and (2) those with alkalosis. Diseases other than hypoparathyroidism responsible for a low serum calcium level are rickets, osteomalacia (including "Arbeiter-tetanie"), steatorrhea (including sprue), chronic diarrhea and chronic renal insufficiency. Alkalosis with resulting tetany is seen in hyperventilation, persistent vomiting, following the administration of certain drugs, etc.

In this paper the clinical data from six patients with chronic idiopathic hypoparathyroidism are presented. Eight more cases which satisfy our diagnostic criteria are abstracted from the literature. The study is concerned not with the effect of the hypoparathyroidism on the body but with the possible cause of the parathyroid pathology. It is obviously a matter of considerable interest what agent could lead to a deficiency of all four parathyroid glands. The case histories are given in the hope that as more cases are recorded some common denominator will appear. One of the seven patients here reported died. This case is presented in more detail and

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the autopsy findings are included. The possible significance of the observed parathyroid gland changes is discussed.

#### EIGHT CASES FROM LITERATURE

If all the factors capable of producing tetany are kept in mind, one finds that most of the cases reported in the literature as "idiopathic hypoparathyroidism," "idiopathic tetany," "essential tetany," etc. are not admissible as proved cases of idiopathic hypoparathyroidism. Careful search of the literature, however, did reveal the following eight cases in which the diagnosis of "chronic idiopathic hypoparathyroidism" seems reasonably justifiable. Transient hypoparathyroidism in new born infants is not considered here (v. case of Pincus and Gittleman<sup>7</sup>). Only those data which might give a clue to the etiology of the disease are recorded.\*

Beumer and Falkenheim,<sup>8</sup> 1926. Three and a half year old boy. Symptoms of tetany for one year. All the signs of tetany on admission. Past and family histories irrelevant. Cod liver oil had been taken without avail. Blood serum calcium, 4.3 mg. per 100 c.c.; blood serum phosphorus, 9.4 mg. per 100 c.c. Roentgenograms showed no evidence of rickets.

Liu,<sup>9</sup> 1928. Forty-six year old Chinese male. Symptoms of three years' duration. Signs of tetany on admission. Serum calcium, 6.0 mg. per 100 c.c.; serum phosphorus, 7.2 mg. per 100 c.c. Blood chlorides and CO<sub>2</sub>, normal. He had had some diarrhea. Ascaris and hookworm ova were found in his stools. Urine analysis, normal. Roentgenograms of bones, normal. Past history, negative. The patient did not improve with cod liver oil or sunlight. Parathormone gave but temporary relief.

Albright and Ellsworth,<sup>10</sup> 1929. Fourteen year old Italian boy with symptoms of tetany since age of eight. Past history of measles and chicken-pox (aged 5). Tonsillectomy (aged 8) just prior to onset of tetany. One attack of carpopedal spasm had been precipitated by a gastrointestinal upset and another by an upper respiratory infection. Physical examination showed classical signs of tetany, teeth in poor condition, early cataracts, enlarged epitrochlear glands, and a palpable spleen (on a later admission). Wassermann reaction, negative. White and red blood corpuscle counts, normal. Basal metabolic rate, minus 6. Plasma calcium, 5.3 mg. per 100 c.c.; plasma phosphorus, 10.8 mg. per 100 c.c. CO<sub>2</sub> combining power of blood, 52.4 volumes per cent. Whole blood chlorides, 80.3 m. eq. per liter. Urine analysis, normal. Roentgenograms of bones, normal.

Leopold and Jonas,<sup>11</sup> 1932. Male, aged 38, with symptoms of tetany of six months' duration. Past history negative except for scarlet fever in childhood. Blood calcium, 5.8 mg. per 100 c.c.; blood phosphorus, 5.4 mg. per 100 c.c. Blood CO<sub>2</sub>, 74 volumes per cent. Patient followed for four years, during which time blood calcium usually was about 6.4 mg. per 100 c.c. and blood phosphorus about 6.0 mg. per 100 c.c.

Cantarow,<sup>12</sup> 1932. Female, aged seven. Attacks of "spasticity" and convulsions since age of three and a half. Constipation and diarrhea for 18 months before entry. Past history of a green stick fracture of right fibula at 18 months, a similar fracture of left fibula at 19 months, and tonsillectomy at three and a half years. No history of rickets. Treatment with vitamin D had been without benefit. Examination showed classical signs of tetany, coarse hair, and dry, thick, puffy skin. Serum

\* The two cases briefly described by Bauer, Marble, and Claflin<sup>6</sup> in 1932 are included in the seven cases herein described.

calcium, 4.8 mg. per 100 c.c.; serum phosphorus, 10.4 mg. per 100 c.c. Blood  $\text{CO}_2$ , 56 volumes per cent. Basal metabolic rate, not reported. Roentgenograms: suggestive of enlargement of thymus; bones normal.

Cantarow,<sup>12</sup> 1932. Female, aged six. Illness started three years previously with attacks of dyspnea, cyanosis, retraction of the abdominal wall, and vomiting, ushered in by a peculiar cry. No history of acute infections or rickets. Obstinate constipation and delayed dentition had been noted. Vitamin D and calcium treatment had been without effect. Examination showed classical signs of tetany, sparse coarse hair, and coarse thickened skin. Serum calcium, 4.2 mg. per 100 c.c.; serum phosphorus, 11.8 mg. per 100 c.c. Blood  $\text{CO}_2$ , 65 volumes per cent. Basal metabolic rate not reported.

Kirklin and Childrey,<sup>13</sup> 1936. Female, aged 19, who had had tetany since seven. Onset followed measles which was complicated by nephritis. Examination showed classical signs of tetany and bilateral cataracts. Serum calcium, 5.2 mg. per 100 c.c.; serum phosphorus, 8.2 mg. per 100 c.c. The urine analysis and the renal function were entirely normal and the blood urea nitrogen was 32 mg. per 100 c.c.\*

Arnold and Blum,<sup>14</sup> 1936. A 38 year old housewife. She had had typhoid fever at 15, an appendectomy "in 1912" which had not relieved her right lower quadrant pain, and colitis with 11 weeks of hospitalization "in 1917" with a recurrence "in 1922." Her general health had declined for seven years before she was seen by the authors. In addition to the signs of tetany she showed tenderness over the sensory nerves, poor teeth, a dry and scaly skin, and thin hair. Serum calcium, 5.4 mg. per 100 c.c.; serum phosphorus, 6.1 mg. per 100 c.c.

#### CASE REPORTS

*Case 1.* B. W., a Russian Jewish tailor, entered the Massachusetts General Hospital July 10, 1926 at the age of fifty-two. He gave a history of having suddenly fallen in the street nine months previously, at which time he did not lose consciousness, but could not arise unassisted because of stiffness, contraction, and numbness of his arms and legs. For 10 weeks prior to admission he had noticed increasing stiffness and cramps of the muscles of his hands, arms, feet, and legs. Three weeks before admission he had had a severe attack associated with loss of consciousness, for which he had been treated at the Boston City Hospital. Since then he had had persistent pains in the shoulders, more marked on the left.

The family history was non-contributory. He knew little about the medical histories of his antecedents. His wife and four children were healthy.

The patient did not recall any previous illnesses. There were no other symptoms than those referable to the neuromuscular system.

Physical examination showed a slightly under-nourished middle aged man with extremities in carpedal spasm. The Trousseau and Chvostek signs were both positive. The initial blood pressure was 88 mm. of mercury systolic, and 70 diastolic, but later observations were always normal. The temperature, pulse and respirations were normal.

Routine urine and blood studies were normal. The nonprotein nitrogen of whole blood was 64 mg. per cent, the sugar 95 mg. per cent, and  $\text{CO}_2$  combining power 71.8 volumes per cent, and the serum chlorides 111 m. eq. per liter. (The nonprotein nitrogen two weeks later was within normal limits, and this was the case on repeated subsequent determinations.) The basal metabolic rate was minus 1 per cent. The serum calcium was 5.1 mg. per 100 c.c.; the serum phosphorus 7.3 mg. per 100 c.c. At a subsequent admission a sugar tolerance test was found to be normal, and the blood cholesterol was 154 mg. per cent. Roentgenograms of the bones were normal;

\* Personal communication from Dr. Oren L. Kirklin.

those of the teeth showed multiple root abscesses. Spinal fluid examination at a much later date gave normal findings. A gastric analysis showed low free acidity.

This patient has been followed since his first admission. The treatment of the hypoparathyroidism is beyond the scope of this paper. Suffice it to say that whenever treatment was omitted the symptoms recurred and the serum calcium and phosphorus levels returned to approximately the values cited above. Cataracts formed and the lenses were removed. The abscessed teeth were removed without any change in the underlying condition. On his tenth and latest admission, in January 1937, his serum phosphatase was found to be 2.8 Bodansky units, his serum calcium 7.1 mg. per 100 c.c., and his serum phosphorus 4.8 mg. per 100 c.c.

*Case 2.* D. B. entered the Out-Patient Department November 20, 1929 at the age of 13, complaining of "fits" at weekly intervals for four years. A diagnosis of "idiopathic epilepsy" was made and the patient was treated with phenobarbital. The attacks continued. The patient was referred to the Ear Clinic because of bilateral chronic otitis media which antedated the onset of the "fits" by about a year. Roentgenograms showed a chronic sclerosing mastoiditis.

On January 8, 1933, the patient was admitted to the hospital for complete study. The history at that time revealed that she had had repeated attacks of stiffness and tingling of the hands and feet for a period of 10 years. These attacks varied in frequency from one every three or four months to five or six attacks a day, being especially frequent after a respiratory infection. Additional symptoms were stiffness of the jaws and rigidity of the whole body. In some of the attacks the patient became dizzy, felt a gripping sensation in the throat, and became unconscious for three or four minutes.

The parents were healthy; three siblings were living and well; and there were no familial diseases.

The past medical history disclosed that she had had measles, chicken-pox, and whooping cough in childhood. Since eight she had had recurrent bilateral otorrhea. Shortly after the onset of this condition a tonsillectomy and adenoidectomy had been performed. Her diet had been adequate in every respect. The menarche had taken place at 13, the menses occurring irregularly every four to five weeks.

Physical examination showed a well developed and nourished 17 year old girl with carpopedal spasm. The Chvostek and Trousseau signs were strongly positive. Both ears were draining. The lenses were clear to the slit lamp examination. The temperature was 98.6°, pulse 80, respirations 25. Examination was otherwise negative. However, on a subsequent examination (January 18, 1934) she had an enlarged liver and a palpable spleen.

Laboratory examinations showed the urine, blood counts, and stools to be normal. The Hinton test for syphilis was negative, the fasting blood sugar 89 mg. per cent, and the nonprotein nitrogen 23 mg. per cent. The serum calcium was 7.0 mg. per 100 c.c. and the serum phosphorus 7.0 mg. per 100 c.c. Additional laboratory data obtained at a subsequent admission showed a normal sugar tolerance curve, a serum phosphatase of 2.5 Bodansky units, a whole blood CO<sub>2</sub> combining power of 58.4 volumes per cent, and three basal metabolic rates of minus 21, minus 13, and minus 21 respectively. A roentgenogram of the chest was normal. The vertebrae, pelvis, femora, and skull were all normal by roentgen examination. Roentgen-rays of the teeth showed the upper third molars unerupted and malposed. The premolars were approximately a centimeter shorter in length than they should be, and the roots were stubby. These dental findings will be discussed elsewhere.<sup>5</sup>

The patient has been followed since. Except when under treatment the condition has remained stationary with about the same degree of hypocalcemia and hyperphosphatemia. A tissue culture of a parathyroid tumor from another patient

was transplanted into the patient's left axilla without any permanent improvement. The patient subsequently became pregnant.

*Case 3.* P. R., a 14 year old American schoolboy of Italian descent, entered the hospital January 24, 1935 with a two months' history of "painful twitchings" of the muscles. Shortly after his admission he had an attack of unconsciousness. After a second similar attack 10 days later the diagnosis of tetany was made. For only two weeks had he been unable to do his work as a newsboy.

The past history showed that in infancy he had been in a hospital for a condition on the back of the head which had healed leaving a scar. Up to two years before entry he had had nose bleeds about once a month. No childhood disease or other previous illnesses were remembered.

His mother was living and well at forty. His father died of a heart attack at thirty-nine. Six siblings were living and well. There was no history of a similar disease in the family.

Physical examination showed a thin, undernourished, 14 year old boy with positive Chvostek and Trousseau signs. The teeth were in poor repair. The blood pressure was 120 systolic and 90 diastolic. The temperature was 99° F., pulse 90, and respirations 20.

Laboratory examinations showed normal urine analysis, normal blood counts, a negative Hinton test for syphilis, serum calcium 4.7 mg. per 100 c.c.; and serum phosphorus 12.9 mg. per 100 c.c. The spinal fluid was negative to the routine tests including the Wassermann.

Roentgenogram of the chest was negative. Roentgenograms of the right wrist and elbow showed normal epiphyses, and bone structure. Roentgenograms of the teeth showed changes which will be described elsewhere.

While in the hospital the patient had *rubella*. This was associated with an eosinophilia of 20 per cent, and occurred before any parathormone was given. The patient later developed erythema nodosum of the legs.

The patient has been followed since. Various forms of therapy have been tried. Without therapy the condition always returned to that seen at the time of the first admission. Cataracts developed for which both lenses were removed.

*Case 4.* W. C., an American school boy, was admitted for the first time March 5, 1936 at the age of sixteen. He gave a four year history of attacks of painless involuntary spasm of the hands and feet associated with a "wooden feeling" or sensation of numbness. On several occasions he had fallen down and had been unable to rise until the spasm had passed off. Running or other forms of exertion precipitated the attacks. Severe attacks had occurred only in the winter.

The mother, aged 58, had hypertension. The father, aged 60, had bronchial asthma and was unable to work. Four brothers and four sisters were living and well. One brother and one sister died quite young of unknown causes. One sister had had rheumatic fever.

Past history was negative except for mumps, chicken-pox, and a tonsillectomy at the age of five.

The physical findings of note were slight undernutrition, opacities in both lenses, and a strongly positive Chvostek sign. Blood pressure was 130 systolic and 80 diastolic.

Laboratory studies showed his urine analysis, blood counts and stools to be normal. The Hinton test was negative. The blood non-protein nitrogen was 23 mg. per 100 c.c.; the basal metabolic rate, minus 4 per cent; the phenolsulphonethalein renal function test, normal. The serum calcium was 6.1 mg. per 100 c.c., serum phosphorus 10.2 mg. per 100 c.c., serum phosphatase 15.4 Bodansky units. Roentgenograms of the skull showed areas of calcification on both sides interpreted as calcification in the choroid plexuses. The sella turcica appeared normal. Roentgenograms

of the long bones, chest, and kidney region were interpreted as being normal. Arterial blood studies by Dr. John H. Talbott showed  $\text{PCO}_2 = 41.0$  vol. %, Tot.  $\text{CO}_2$  of true plasma = 58.8 vol. %,  $\text{pH}_s = 7.41$ . These values were normal and ruled out alkalosis.

The patient has been followed since but no additional data concerning the etiology of the disease have been obtained. When not receiving treatment he quickly reverts to the state observed at the time of entry.

*Case 5.* The following case history was very kindly supplied by Dr. Roy F. Farquharson from the Toronto General Hospital.

The patient, a Russian Jew of 44, entered the Toronto General Hospital in February 1929, because of symptoms of tetany. His illness started two months before admission at which time he and other members of his family suffered an acute illness which was diagnosed as influenza. Symptoms consisted of malaise, fatigue, generalized aching, and a hyperpyrexia of  $100^\circ$  F. and over. The symptoms of tetany started four days following the onset of this illness and persisted until admission.

On physical examination he presented the typical picture of a patient with fairly severe tetany. Otherwise the examination was not remarkable except for dental sepsis.

Roentgenograms of the sinuses showed some involvement of both antra. The roentgenograms of the bones were not remarkable except for some osteoarthritis of the spine.

He was seen from time to time up to January 1935. The tetany persisted. The serum calcium was always low—4.4 to 7.0 mg. per 100 c.c., and the serum phosphorus was always high—6.2 to 7.3 mg. per 100 c.c. His urine examinations were always entirely negative.

#### CASE WITH AUTOPSY

*Case 6.* A. P., a boy of five, first entered the hospital October 5, 1926 with a history of convulsions once or twice a week for nine months.

The family was American; the parents were healthy, two siblings aged one and three years were normal; and no family diseases were known.

The patient was born prematurely at  $7\frac{1}{4}$  months. The mother was a nullipara and labor had lasted 16 hours, being terminated by instrumental delivery. The infant weighed five lbs. but was healthy, and was breast fed for 10 months. Dentition began at two months and walking at one year. The patient had pertussis at two and measles at four years.

The present illness began approximately one year prior to entrance at which time he developed pains in the right foot with some degree of inversion. Shortly thereafter the patient's parents noted that he handled a fork or spoon awkwardly. Nine months before entry he had the first convulsion. Thereafter, these occurred about once a week, increasing to twice a week during the month prior to entry. A typical convulsion was described as starting with abdominal pain followed by general tonic rigidity of the body and extremities with retraction of the head and cyanosis. Events during the attack were lost from memory. For 10 months his appetite had been poor.

Physical examination showed red marks on the face suggesting impetigo scars, dental caries, pyorrhea, palpable epitrochlear lymph nodes, and absent knee jerks. The temperature was  $98^\circ$  (R), pulse 80 to 110, respirations 20 to 35 per minute.

Laboratory tests showed the urine, blood counts, stool, and spinal fluid to be normal. The Wassermann and tuberculin tests were negative, and the Schick test positive. Roentgenograms revealed no abnormalities of the skull and no enlargement of the thymus region.

The patient was discharged two weeks after admission to the Out-Patient Department with a presumptive diagnosis of epilepsy, but one month later was readmitted with the history that since discharge the convulsions had continued at intervals

of a week or two, and that at night he had breathed with a crowing sort of inspiratory sound. The stiffness and spasm of his hands and feet had increased.

This time the patient showed exaggerated deep reflexes, carpopedal spasm, Chvostek and Trousseau's signs. Again the urine analysis, blood counts, Wassermann reaction, and spinal fluid were normal. A sugar tolerance test was normal. The serum chlorides were 103 m.eq. per liter, and the  $\text{CO}_2$  combining power 59.5 volumes per cent. The tuberculin test had become positive in 1:1000 dilution. The serum calcium was 5.2 mg. per 100 c.c., and the serum phosphorus 12.0 mg. per 100 c.c. Roentgenograms of the skull, sella turcica, and hands were normal. Blood cholesterol was 256 mg. per 100 c.c. The basal metabolic rate was minus 8 per cent. Electrocardiogram showed sinus arrhythmia.

The patient was given 1 gm.  $\text{NH}_4\text{Cl}$  daily and in 11 days the tetany had stopped. The  $\text{CO}_2$  combining power was lowered to 48 volumes per cent. Following this he received 2 c.c. of 50 per cent  $\text{CaCl}_2$  and  $\frac{1}{2}$  grain desiccated thyroid daily. No further convulsions occurred. He was discharged June 16, 1927 on this regime.

During the next year and a half he remained comfortable while on this treatment, but any cessation of it resulted in severe attacks of tetany.

He was admitted for the third time February 18, 1929. The findings were as before except that following parathormone administration he developed an eosinophilia of 8 to 11 per cent. The patient was very thoroughly studied for nearly five months, during which time the effect of parathormone, ammonium chloride, and irradiated ergosterol was evaluated. The best results were obtained with a combination of  $\text{CaCl}_2$  and irradiated ergosterol. On July 6, 1929 he was discharged on the following regime: 50 per cent  $\text{CaCl}_2$ —drams 1, three times daily; Vigantol—5 drops daily; thyroid extract (Armour)—gr. 1 daily; and high calcium diet. The patient did very well on this regime but gradually discontinued one measure after another until finally his only treatment was 50 per cent  $\text{CaCl}_2$  1 dram twice a day. For five years he managed fairly well without other treatment. During this time he had one or two convulsions a year, and noted stiffness of the hands and feet about once every two months. He noted increasing constipation during this period.

On the final admission, September 23, 1934, he complained of abdominal pain and persistent vomiting of two to three weeks' duration. He was found to have otitis media and to be very toxic, with a swinging temperature up to  $104^\circ$ . After drainage of the ear he showed a poor clinical and leukocytic response. Septicemia and metastatic abscesses of the back and a purulent arthritis of the knee supervened. He died of sepsis October 11, 1934.

#### POSTMORTEM EXAMINATION

Exclusive of the changes found in the parathyroids, the significant necropsy findings were subcutaneous abscesses of the back and thigh and septic arthritis of both knees. Postmortem blood cultures showed *Streptococcus hemolyticus* and *Staphylococcus aureus*.

Grossly, all four parathyroids were easily demonstrated. They were normal in size, each measuring approximately 6 by 3 by 2 millimeters. The surfaces were smooth and very pale brown in color. There was no question in the minds of the many observers that the glands demonstrated were characteristic of parathyroid tissue. Two of the glands were fixed in Zenker's fluid, one in 10 per cent formalin and one in absolute alcohol.

Microscopically, all the parathyroid parenchyma in all four glands was replaced by fat cells (figure 1). The normal architecture of the gland was still present, there being a well-outlined fibrous connective tissue capsule. The pericapsular tissue was composed of fat cells in which were scattered large vessels filled with red blood cells,

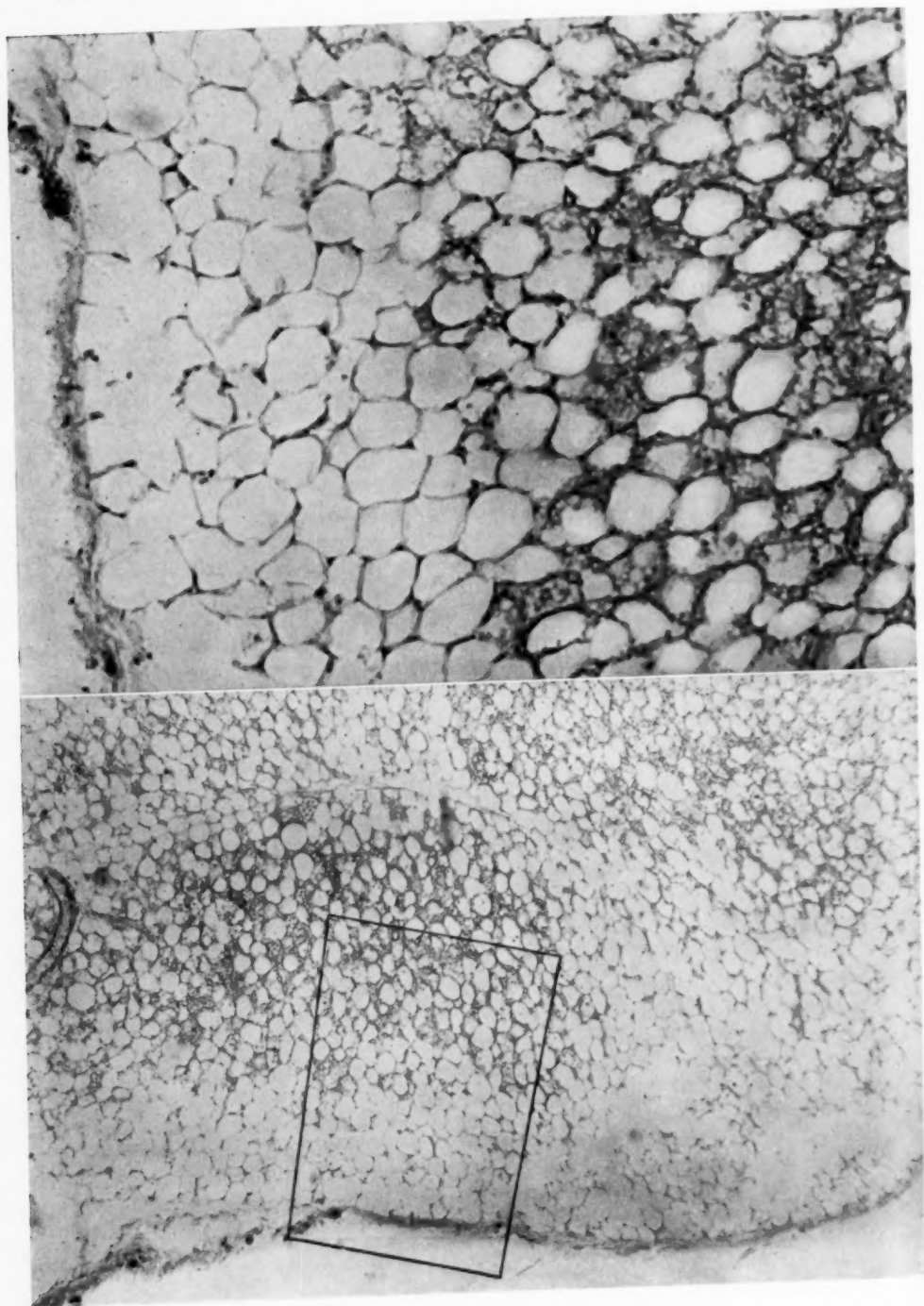


FIG. 3. High and low powered photomicrographs of parathyroid tissue from Case 1.

a picture that is seen in the normal gland. The appearance of the fat cells in and about the peripheral fifth of the gland was quite different from that seen in the central four-fifths. In this outer zone each fat cell was outlined by a sharp, thin, acidophilic membrane and was contiguous to several similar cells, the intervening stroma being practically absent except for an occasional small, flattened, basophilic cell. This fat tissue was in all respects similar to that deposited between parathyroid cells in the normal adult gland. The cells were all equal in size and no parathyroid epithelial cells could be identified between them. The remainder of the gland was composed of fat cells of varying sizes with definitely more intercellular stroma. This increased stroma was found to be composed for the most part of cells containing much smaller fat droplets. The majority of these cells were about the size of a normal parathyroid cell; some, indeed, contained very tiny droplets similar to those often seen within the normal chief cell. In addition there were between the larger fat cells irregular deposits of light, eosinophilic, amorphous material, a finding that is occasionally seen within cystic spaces of normal parathyroid glands. The connective tissue cells in the stroma were definitely increased. The vascular supply of the stroma was similar to that observed in the normal gland.

It was difficult to determine whether any of the cells observed were normal parathyroid cells. There were scattered single cells which closely resembled chief cells, but the fact that they occurred singly made it extremely difficult to be certain that they were. Occasional dark oxyphil cells, such as one observes in the normal gland, were seen close to the stroma. All the fat cells described stained with Scharlach R. No glycogen granules were seen.

It was thought that the above described findings showed definitely that the specimens studied were the remains of the parathyroid glands and not pieces of fat mistaken for parathyroid tissue, an objection that might be raised. The glands were identified and removed by one of us (B.C.) who had previously removed and studied the glands from approximately 200 necropsies. It did not seem possible that an error in recognition could have been made in the case of all four glands. The presence of a definite capsule, the distribution of the fat cells, the possible presence of a few chief cells and the finding of definite dark oxyphil cells would seem to be sufficient evidence to prove that the specimens examined were parathyroid glands. The absence of glycogen was to have been expected in non-functioning cells.

All the glands of internal secretion were examined but no other marked abnormalities were noted. There was a diffuse lymphocytic infiltration of the pancreas. It was thought that there was a diffuse, moderate increase in the basophilic cells in the pituitary.

#### DISCUSSION

The clinical findings in 14 cases (eight from the literature and six here reported) of idiopathic hypoparathyroidism have been reviewed. The autopsy findings of fatty replacement (?) of the parathyroid epithelial cells in one of our cases have been presented. A careful search of the literature has revealed no similar example.

Increase of the interstitial fatty tissue of the parathyroid glands has long been known to occur with age (Benjamin<sup>15</sup>, Erdheim<sup>16</sup> and von Verebely<sup>17</sup>). It is the experience in this hospital that fat cells begin to appear in the normal parathyroid after puberty and increase in number up to middle age. A gland from an individual 40 years of age usually has a fat content between 30 and 50 per cent. As has often been pointed out it is inexact

and loose nomenclature to refer to these changes as "fatty degeneration." A more suitable term probably is "fatty replacement." The situation may be quite analogous to that in the bone marrow, where the fat cells merely fill up the space not taken by the hematopoietic tissue or give way to that tissue when there is hyperplasia. It is not at all certain, however, that the changes in the case here described represent the limiting degree of this fatty replacement. It is rather believed, on the other hand, that some obscure degenerative process must have been present as well. The pathology is not to be confused, furthermore, with what Herxheimer<sup>18</sup> calls "lipomatosis of the parathyroids" which is nothing more than a fatty infiltration of the stroma of the glands, such as may occur in any organ, especially in those of an obese individual.

The findings in another case which has been recently autopsied at the Massachusetts General Hospital and which will be reported in detail by Castleman and Hertz<sup>19</sup> are pertinent to the above discussion. The patient was a woman of 48 with clinical evidence of marked hypothyroidism and hypopituitarism. Hypoparathyroidism was not suspected and so blood calcium studies were not done. Autopsy showed sclerosis of the anterior pituitary and atrophy of all the endocrine glands. The parathyroid glands showed almost complete replacement of the epithelial cells by fat cells (figure 2). This was simple "fatty replacement" due to epithelial atrophy. There was no suggestion of a degenerative process.

It is impossible, of course, to know whether all the cases of idiopathic hypoparathyroidism will have the same pathology. The following review of lesions found in the parathyroid glands which might cause hypofunction seemed of interest. No other case of demonstrated idiopathic hypoparathyroidism with autopsy findings has been found.

According to Herxheimer<sup>18</sup> no case of complete aplasia of the parathyroids has been recorded. Hypoplasia, however, has been described by Boettiger and Wernstedt<sup>20</sup> in a four month old infant dying of tetany, in whom the parathyroids were so minute they could be found only by serial sections of the tissue of the neck. Haberfeld<sup>21</sup> described hypoplasia of the parathyroids in a 25 year old man dying of typhoid fever who had tetany during his illness. He interpreted this to mean that the patient had enough parathyroid tissue to prevent tetany until the stress of an acute infection occurred. Atrophy of the parathyroids, without some obvious cause such as hemorrhage, fibrosis, syphilis, and so forth, has not been reported.

A large number of focal lesions has been described which could hardly be considered as an adequate explanation of chronic hypoparathyroidism. These include hemorrhages,<sup>22, 23, 24, 25, 26</sup> bacterial emboli,<sup>23, 24</sup> cysts,<sup>18, 24</sup> and malignant invasion.<sup>28, 37</sup> Various tuberculous lesions<sup>15, 27, 17, 28, 24, 29</sup> are on record, but little importance can be attached to them. Rheumatic<sup>30</sup> and suppurative parathyroiditis<sup>31</sup> are probably of academic interest only.

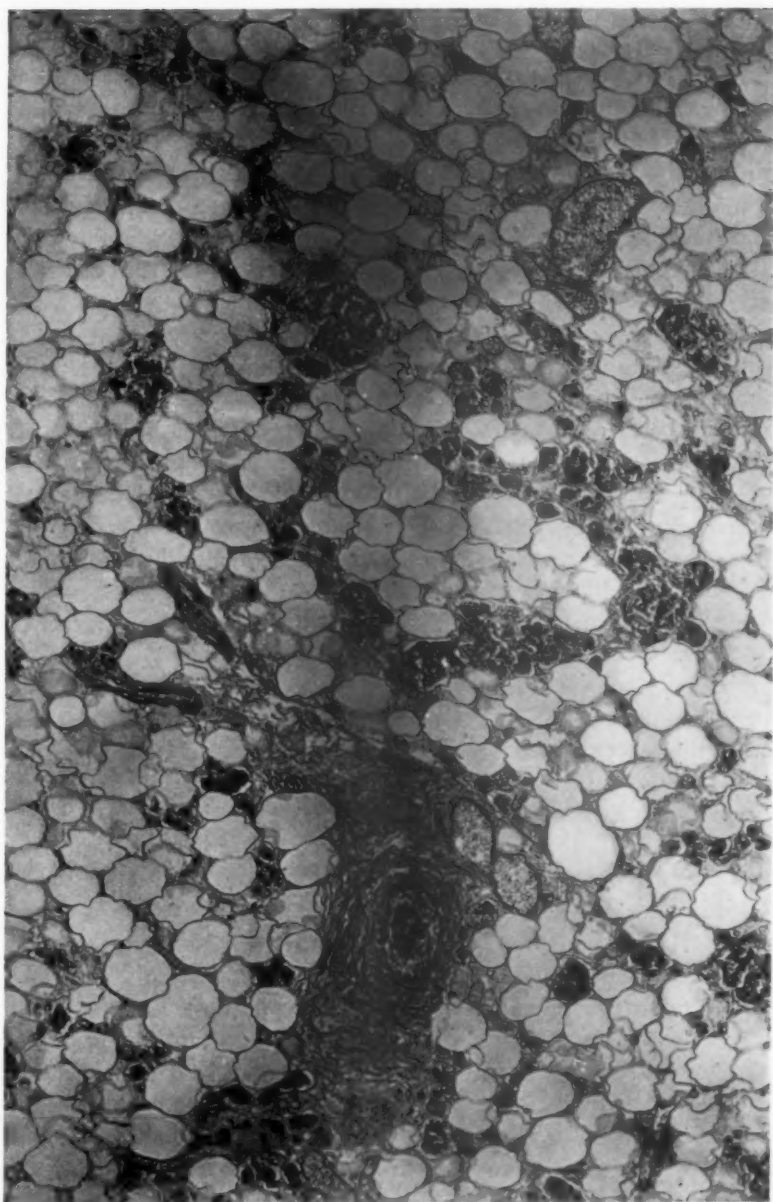


FIG. 2. Photomicrograph of parathyroid tissue from case of Hertz and Castleman. Note few remaining islands of epithelial tissue, in contrast to figure 1 where no epithelial tissue is present.

The evidence for syphilis is slightly more impressive. Haberfeld<sup>21</sup> described a case of a six weeks old infant with congenital syphilis in whom the parathyroids showed hemorrhages, old blood cysts and atrophy of the parenchyma. No mention was made of whether or not tetany had been present. Lindemann<sup>32</sup> also described what he interpreted as syphilitic atrophy. Kraus<sup>33</sup> in a newborn infant with syphilis reported the finding in the parathyroids of a chronic productive interstitial inflammation including parenchymal atrophy, lymphocytic and larger mononuclear infiltration. Langeron<sup>34</sup> and his collaborators described the case of a 47 year old mason who had had recurrent tetany for five months before death. The blood calcium was low. At autopsy gummata of the lungs were found. The two external parathyroids were examined and found to be yellower and larger than normal. The one parathyroid examined microscopically showed diffuse sclerosis. This case cannot be accepted as one of proved parathyroid insufficiency because no phosphorus studies were done. References to other French works on syphilis of the parathyroids may be found in this article.

Dieterich<sup>30</sup> reviews the subject of parathyroid lesions in acute infections and comments on the scarcity of observed parathyroid lesions in the infectious diseases (scarlet fever, measles, diphtheria, typhoid, etc.). Garnier<sup>35</sup> found degenerative changes in two cases of scarlet fever. Bojew<sup>36</sup> in 1926 injected nine dogs with varying doses of diphtheria toxin. In some, spastic motions occurred two to 12 days later. Various changes were observed in the parathyroids, including vascular dilatation, effusion of blood, hydropic degeneration and necrosis of cells. The lesions were well illustrated; unfortunately there were no blood chemical studies.

Fibrosis of the parathyroids occasionally occurs, but is usually secondary to conditions such as syphilis, tuberculosis, or lymphoma. Haberfeld, however, found fibrosis (scarring) of two glands, round cell infiltration in a third, and atrophy in the fourth in a woman dying in pregnancy with tetany.

Amyloidosis<sup>18, 21</sup> and chronic passive congestion<sup>23, 21</sup> do not concern this discussion. Hydrops of the parathyroid glands in association with what was interpreted as mild inflammation has been reported.<sup>15</sup>

It is probably of little value to attempt to explain one disease of unknown etiology by comparing it with another. However, attention should be called to the disease entity in which all parathyroid tissue is tremendously hypertrophied and in which there is accompanying hyperparathyroidism.<sup>38, 39</sup> This disease must be due to some disorder. It is just possible that the disease under discussion is due to a disturbance at the same place in the opposite direction.

A survey of the 14 cases of idiopathic hypoparathyroidism cited above reveals surprisingly little of etiological significance. There was nothing in the histories to suggest an hereditary factor. There were nine males and five females. The ages of onset suggest that there are two groups, a childhood and adolescent group and an elderly group. The actual ages were 2½, 3, 3½, 4, 7, 8, 9, 12, and 14 and 38, 41, 43, 44, and 52. It should be

noted that there is a gap of 24 years between the age of 14 and that of 38. It is perfectly possible that the cause of the disease in the two groups will be found to be entirely different. The disease once established apparently remains permanently. In several of the cases the disease was precipitated by an acute infection. Thus the boy of 14 reported by Albright and Ellsworth had a tonsillectomy just prior to the onset of the tetany. The same was true of Cantarow's girl of seven. Kirklin and Childrey's patient developed tetany following measles and a complicating nephritis. Case 6 likewise developed tetany shortly after the measles. Case 2 was suffering from bilateral otitis media at the time of onset of her tetany, and case 5 developed tetany during an attack of "influenza." The above facts, coupled with the observations showing parathyroid degenerative changes in acute infections<sup>35, 23, 24</sup> suggest that bacterial or virus agents may be etiologically responsible for some cases of idiopathic hypoparathyroidism. However, it must be remembered that infections are apt to precipitate the symptoms of tetany in latent tetany.

#### SUMMARY AND CONCLUSIONS

The criteria necessary for a diagnosis of chronic idiopathic hypoparathyroidism are set forth. These should include low serum calcium and high serum inorganic phosphorus levels, normal bone texture by roentgenogram, and the absence of renal insufficiency.

Eight cases of the disease collected from the literature are cited and six new cases are added.

The autopsy findings are given in one fatal case. The parathyroid glands were normal in size but histologically all the epithelial cells were entirely replaced by fat cells, a finding heretofore not recorded in parathyroid pathology. No other clinically proved case with an autopsy was found in the medical literature.

A survey is made of the pathological lesions previously reported which could conceivably interfere with parathyroid function.

The possibility is mentioned that idiopathic hypoparathyroidism may be the antithesis as regards the parathyroid disorder of idiopathic hypertrophy of the parathyroids with hyperparathyroidism.

Attention is called to the fact that the disease usually starts in childhood or adolescence and, if not then, not until about forty. In several instances the onset was closely related to acute infections. The possibility of some bacterial or virus infection injuring the glands is discussed.

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## ESSENTIAL HYPERTENSION AND CHRONIC HYPERTENSIVE ENCEPHALOPATHY

### (A Clinico-Pathologic Study) \*

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THE associated renal and cardiac lesions of essential hypertension are well known; the neural complications, however, are less well established. The question frequently arises whether the neurological symptoms are caused by cerebral hemorrhages as a result of rupture of diseased vessels, encephalomalacias from thrombosis of the larger atherosclerotic cerebral vessels or encephalopathic changes secondary to implication of the cerebral arterioles. Our cases showed arteriolar involvement and clinical symptoms characterized by headaches, dysesthesias, fleeting paralysis, personality changes, intellectual impairment and a prolonged progressive course. The term "chronic hypertensive encephalopathy" is most appropriate for this group because of the diffuse areas of demyelination, focal hemorrhages and areas of devastation. In a series of seven cases of essential hypertension, all showed such changes. This condition should not be confused with "hypertensive encephalopathy" described by Fishberg,<sup>1</sup> characterized by sudden cerebral vasoconstriction associated with acute episodes of sudden marked elevations of blood pressure, severe headaches and convulsions. A reevaluation and reinterpretation of this subject in the light of the pathologic changes reported in the literature and those shown in our cases are of importance.

#### CASE REPORTS

*Case 1.* B. L., a man, aged 35, was admitted to the Montefiore Hospital on January 3, 1929. For four years (1916 to 1920), the patient suffered from attacks of nausea, numbness, inability to speak, stiffening of the mouth and coldness of the extremities. These episodes would last 15 to 20 minutes, were not associated with loss of consciousness and were followed by generalized weakness lasting for one to two days. The patient was well from 1920 to 1925. In April 1925 there developed weakness of the right side of the face and right arm, aphasia and difficulty in swallowing. Examination at that time revealed hypertension. After three months progressive mental deterioration was noted but the aphasia cleared up partially.

*Physical Examination:* Examination revealed enlargement of the heart to the left and gangrene of the toe. The blood pressure was 190 systolic and 130 diastolic.

*Neurological Examination:* The patient was unable to walk. There were bilateral hyperreflexia, Babinski toe signs, ankle clonus and absent abdominal reflexes. Partial aphasia and questionable apraxia and agraphia were present. The speech was dysarthric. The sensory examination was unreliable. The optic fundi showed moderate arterial spasm. There was a left homonymous hemianopsia. The pupils were unequal and irregular; the left did not react to light and the reaction of the right

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was sluggish. There was a right supranuclear facial paresis. The patient was inattentive, irritable, uncoöperative and showed marked intellectual deterioration.

*Laboratory:* The maximum specific gravity of the urine was 1.019. Hemoglobin 80 per cent. The urea nitrogen was 23.6 mg. per cent on admission but rose to 72 mg. per cent just before death. The blood Wassermann reaction was negative.

*Course:* The blood pressure varied greatly, at times dropping to 120 systolic, 80 diastolic with subsequent rises to its previous level. At one time it reached 210 systolic, 140 diastolic. On May 11, 1929, the patient had a clonic convulsion lasting 10 minutes and involving the right upper and lower extremities. Several days later bronchopneumonia set in and he died on May 16.

*Anatomic Diagnosis:* Cerebral arteriosclerosis, arteriolosclerosis of the kidneys with subacute malignant changes; cardiac hypertrophy; hemorrhagic bronchopneumonia; fibrinopurulent pericarditis.

*Autopsy of the Nervous System:* The brain was edematous. Horizontal sections disclosed areas of softening in the right temporal and occipital convolutions and of the left third frontal, pre- and postcentral convolutions and the internal capsule (figure 1). Small areas of destruction were present throughout the centrum ovale of both hemispheres.

*Microscopic Examination:* Examination of the involved cortical convolutions stained by the cresyl violet method revealed circumscribed areas of destruction (figure 2 A), distortion in the arrangement of the cyto-architectural layers (figure 2 B), almost complete loss of ganglion cells and endothelial proliferation of capillaries (figure 2 C). Small areas of devastation surrounded the smaller arterioles. The ganglion cells in these areas showed all types of pathologic changes, such as sclerosis, calcification, ischemia, chromatolysis and complete destruction. The white matter contained small areas of softening filled with compound granular corpuscles, scattered areas of devastation, collections of glia cells and glia nodules. The larger vessels showed arteriosclerosis with intimal proliferation. The precapillary arterioles revealed narrow lumina, marked hypertrophy of the media with an increase in the number of nuclei. Hyalin changes in the media were also present.

*Comment:* The onset of the symptoms 13 years before death, the predominance of the cerebral symptoms throughout the course of the illness, the presence of diffuse cerebral lesions and the changes in the precapillary arterioles were the outstanding features. There was some evidence of renal involvement as indicated by the limitation in the concentrating power of the kidney. The terminal rise in blood urea was probably the result of the severe bronchopneumonia.

*Case 2.* B. N., a woman, aged 38, was admitted to this hospital on June 3, 1931, complaining of severe headaches and occasional attacks of dizziness. She suffered from diabetes and hypertension for several years. In August 1931 a right-sided hemiplegia developed; this cleared up partially. On June 20, 1931, the patient experienced a sensation of "something falling on the left side of her head." A few hours later blindness, which lasted a few days, appeared. Vision improved gradually, but never completely.

*Physical Examination:* Examination on admission revealed an enlarged heart and a blood pressure of 275 systolic and 170 diastolic. Fundus examination showed copper wire tortuous arteries with retinal hemorrhages in the left eye.

*Neurological Examination:* Examination disclosed a slight right-sided weakness with hyperreflexia, a questionable Babinski sign, diminished right abdominal reflex and a slight right facial weakness. The left pupil was larger than the right and both reacted sluggishly to light.

*Laboratory Data:* The maximum specific gravity of the urine was 1.021. Albumin was present in amounts varying from a trace to two plus. The glucose in the urine was negative. Glucose tolerance test gave a diabetic curve with a peak of



FIG. 1. (Case 1.) Area of destruction of the right motor region and the Island of Reil. Notice numerous areas of destruction throughout the white matter.

347 mg. per cent two hours after the administration of the glucose. Urea nitrogen was 17.1 mg. per cent. The Wassermann reaction of the blood was negative.

*Course:* On June 22, 1931, there developed a left-sided convulsion followed by a left hemiplegia, unconsciousness, projectile vomiting and cyanosis. Examination at

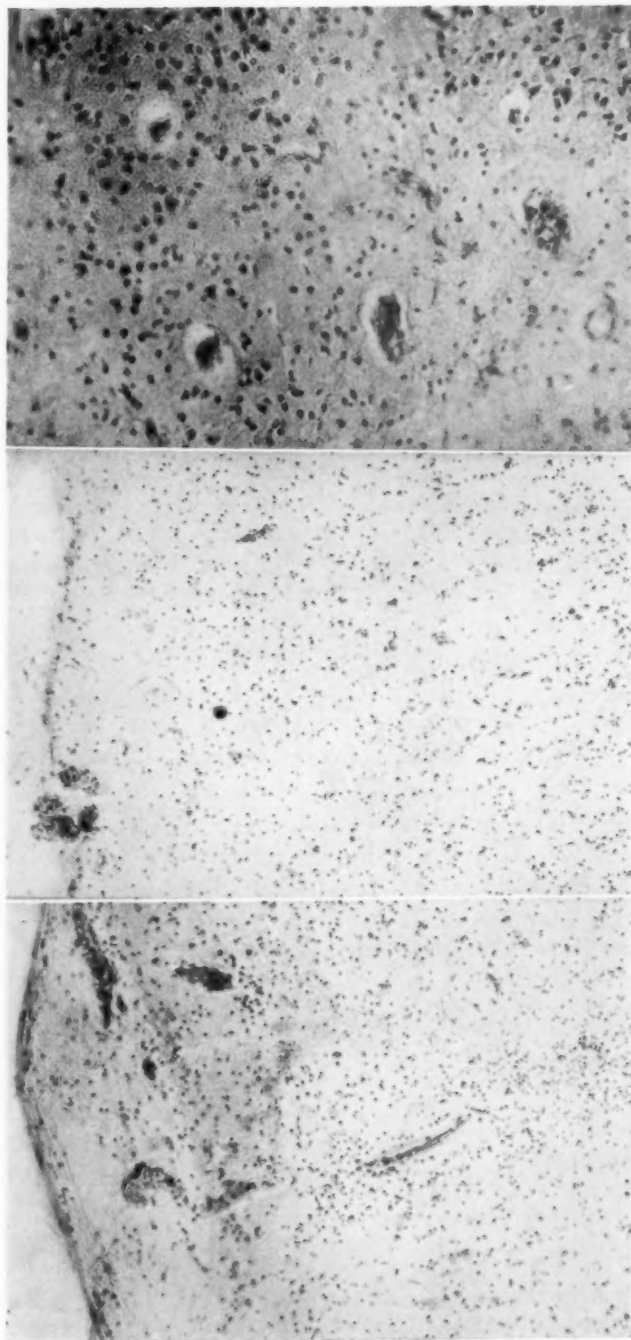


FIG. 2 A.

FIG. 2 A. (Case 1.) *Left*. Small area of softening with destruction in the arrangement of the cyto-architectural layers. Cresyl violet  $\times 50$ .

FIG. 2 B. (Case 1.) *Center*. Distortion in the arrangement of the cyto-architectural layers with dropping-out of nerve cells. Cresyl violet  $\times 50$ .

FIG. 2 C. (Case 1.) *Right*. Area of devastation with endothelial proliferation of the cortical vessels. Cresyl violet  $\times 100$ .

FIG. 2 B.

FIG. 2 C.

that time revealed generalized flaccidity with hyperreflexia, absent abdominal reflexes and bilaterally positive Babinski signs. A lumbar puncture revealed bloody fluid. Patient died shortly afterward.

*Anatomic Diagnosis:* Cerebral arteriosclerosis; thrombosis of branches of the middle cerebral artery; rupture of pontine branches; coronary sclerosis; hypertrophy and dilatation of the heart; arteriosclerosis of the kidneys.

*Autopsy of the Nervous System:* There was marked atherosclerosis of the vessels at the base of the brain. A subarachnoid hemorrhage was present over the temporal lobes, the peduncles and the cerebellum. An area of softening was noted in the left caudate nucleus and pulvinar. A fresh pontine hemorrhage extended caudally into the medulla oblongata and cerebellum.

*Microscopic Examination:* In the myelin sheath preparations, numerous small areas of softening involved the left corona radiata near the corpus callosum, the internal capsule, and the medial and lateral thalamic nuclei (figure 3 A). The right caudate and thalamus were the seat of small areas of cystic degeneration. In the sections stained by the cresyl violet method, some of these areas had a honey-combed appearance (figure 3 B), were filled with compound granular corpuscles, proliferating vessels and slight fibroblastic reaction. The small arterioles were thickened and showed beginning hyalinization of their walls; there was diminution in the size of the lumen. Sections of the pons disclosed a massive hemorrhage destroying most of the pontine fibers, the medial lemniscus, the thalamo-olivary and rubro-spinal tracts and the trapezoid body. The fourth ventricle was filled with blood. A section of the cerebellum stained by the cresyl violet method revealed a glia nodule in the white matter of the left hemisphere.

*Comment:* The headaches and dizziness from which the patient suffered for several years before her death, were undoubtedly secondary to disturbances in the cerebral circulation as expressed in the form of focal areas of softening. The temporary hemiparesis and visual complaints were also caused by the advanced arteriolar disease. The pontine hemorrhage was the cause of the death. The course of this patient's hypertension was characterized essentially by symptoms of progressive cerebral involvement.

*Case 3.* J. T., a man, aged 28, was admitted to this hospital on February 25, 1932, with a history of dizzy spells since 1930. Later the patient complained of malaise, occasional nausea and vomiting and diplopia. A diagnosis of malignant hypertension was made. On January 1, 1932, there developed a right hemiplegia and marked emotional lability.

*Physical Examination:* Examination revealed peripheral arteriosclerosis, an enlarged heart, bilateral papilledema with thickening of the arterioles, and a blood pressure of 180 systolic and 130 diastolic.

*Neurological Examination:* Examination disclosed pathological laughter and crying; right spastic hemiplegia with pyramidal tract signs; spastic left lower extremity with a positive Babinski toe sign; irregular pupils, the left larger than the right, both reacting sluggishly to light; bilateral weakness of the muscles supplied by the fifth nerve; complete paralysis of the right seventh nerve; paralysis of the palate; incomplete protrusion of the tongue, evidence of bilateral involvement of the eleventh nerve and urinary and fecal incontinence.

*Laboratory Data:* The urine concentrating power was good. The presence of albumin was detected once. Hemoglobin 85 per cent. The blood urea nitrogen was normal. The Wassermann reactions of the blood and spinal fluid were negative.

*Course:* The patient developed bronchopneumonia and died on October 4, 1932.

*Anatomic Diagnosis:* Generalized arteriosclerosis; arteriolosclerosis of the brain,

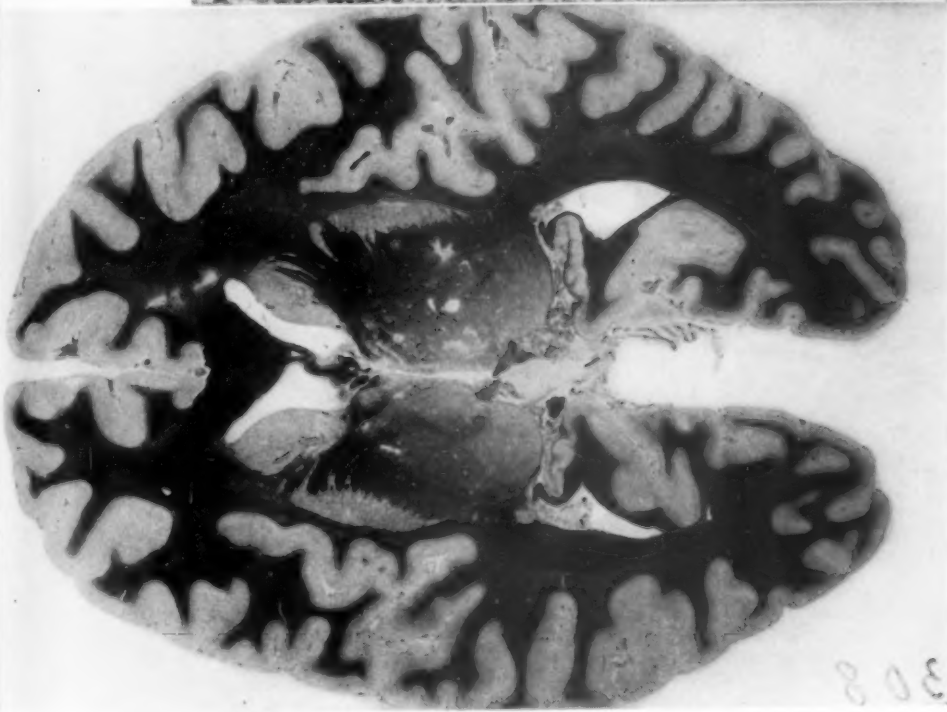


FIG. 3 A.

FIG. 3 A. (Case 2.) *Left.* Small areas of softening involving the corpus callosum, internal capsule, and the medial and lateral thalamic nuclei.

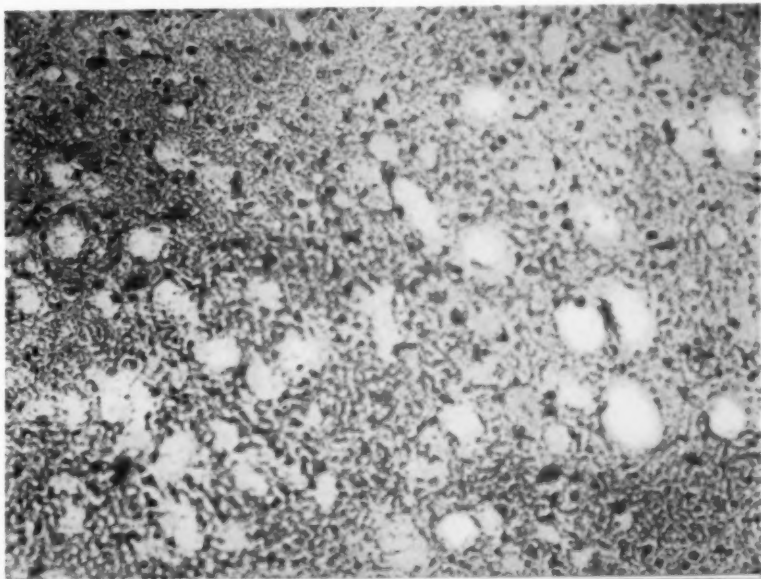


FIG. 3 B.

FIG. 3 B. (Case 2.) *Right.* Honey-combed appearance. Cresyl violet  $\times 100$ .

kidney, spleen, heart, pancreas, testicles and psoas muscle; hypertrophy of the heart; bilateral lobar pneumonia.

*Autopsy of the Nervous System:* Examination of the brain revealed marked atherosclerosis of the vessels of the circle of Willis. A large area of softening destroyed the inferior portion of the left internal capsule and parts of the caudate and putamen. Another area of softening on the right involved the external seg-



FIG. 4. (Case 3.) Medium sized arteriole showing marked endarteritic changes with obliteration of the lumen. Resorcin-fuchsin  $\times 50$ .

ment of the globus pallidus, putamen, internal capsule and pulvinar. Punctate hemorrhages were found in the tip of the right caudate and medulla oblongata.

*Microscopic Examination:* In the myelin sheath preparation, in addition to the large areas of softening, there were also numerous small areas of demyelination. The cerebral vessels showed marked proliferation of the intima and splitting of the internal elastic lamina. The medium-sized arterioles and capillaries showed marked endarteritic thickening, with practically complete obliteration of the lumen (figure 4).

*Comment:* This case is of interest because of the similarity in the alterations of the arterioles throughout all organs. The main clinical signs and pathologic changes were those referable to the central nervous system.

*Case 4.* S. L., a man, aged 38, was admitted to this hospital on November 2, 1935, with a history of hypertension of three years; headaches and nocturnal dyspnea of one year, increasing pallor and loss of weight of six months' duration and difficulty in speech and weakness of the right side of the body one day prior to admission.

*Physical and Neurological Examination:* The patient was somnolent and pale. The heart was enlarged. The blood pressure was 250 systolic and 170 diastolic. Marked peripheral and retinal sclerosis with hemorrhages and exudates was noted. The right pupil was larger than the left. There was a flaccid right hemiplegia and motor aphasia.

*Laboratory Data:* The urine showed a specific gravity of 1.018, 4 plus albumin, and numerous casts with occasional red blood cells and white blood cells. The Wassermann reaction of the blood was negative. The spinal fluid pressure was 260 mm. of water. The blood urea nitrogen was 37.2 mg. per cent and it rose terminally to 55 mg. per cent.

*Course:* On November 26, 1935, the patient became drowsy and developed a global aphasia. Two days later he had a convulsion and died.

*Anatomic Diagnosis:* Generalized arteriosclerosis with involvement of brain, kidney and coronary vessels; rupture of branches of the left middle cerebral and basilar arteries; cardiac hypertrophy and dilatation.

*Autopsy of the Nervous System:* The vessels at the base of the brain showed marked atheromatous plaques. There was a hemorrhage in the region of the left insula and basal ganglia. Hemorrhages were present in the pons, destroying the greatest part of the tegmentum and in the medulla oblongata.

*Microscopic Examination:* In the myelin sheath preparation, the left centrum ovale stained poorly. The large hemorrhage destroyed the left insula, internal capsule and basal ganglia. The involved convolutions revealed a loss in the arrangement of the cyto-architectural layers. Ring hemorrhages were found in areas adjacent to the massive hemorrhage. The ganglion cells showed various pathologic changes; the ischemic cell changes were the most prominent. Smaller areas of demyelination in other regions with relative acellularity and an occasional glia nodule were seen. The capillary walls throughout the nervous system were thickened while the small arterioles showed early hyalin degeneration of the media with an increase in the thickness of its wall and narrowing of its lumen. The perivascular spaces appeared dilated in many areas; the adjacent brain tissue was edematous. Perivascular gliosis was also present.

*Comment:* This case illustrates the simultaneous involvement of kidney, heart and brain with death from cerebral lesions. Although the neurologic signs indicated involvement of the left middle cerebral artery, lesions were found throughout the central nervous system.

*Case 5.* I. W., a woman, aged 40, was admitted to this hospital on August 25, 1932, with a history of severe frontal headache and hypertension for eight years. During the last four years, the patient had attacks of numbness on the left side of the body, associated with blurring of vision. In January 1932, she complained of severe abdominal pain and vomiting and lost 30 to 40 pounds in weight in one month.

*Physical and Neurological Examination:* The patient was emaciated. The peripheral vessels were moderately sclerotic; the heart was enlarged. The blood pressure was 190 systolic and 120 diastolic. The fundi showed bilateral papilledema, more marked on the right, thickened retinal arteries, and numerous exudates and flame-

shaped hemorrhages. There was a slight left hemiparesis with a positive Babinski toe sign on that side and a normal plantar response on the right.

*Laboratory Data:* Examination of the urine disclosed a specific gravity of 1.018, 4 plus albumin, numerous casts with a few white blood cells and occasional red blood cells. The hemoglobin was 54 per cent. There were 2,500,000 red blood cells. The blood urea on admission was 23 mg. per cent.

*Course:* On September 3, 1932, the patient vomited and complained of severe frontal headache. The blood pressure at that time had risen to 270 systolic and 160 diastolic. She became drowsy and later semi-stuporous. Examination at this time revealed a left homonymous hemianopsia, hypesthesia on the left side of the body, slight neck rigidity and a suggestive Brudzinski sign on the right. Lumbar puncture yielded clear fluid under a pressure of 240 mm. of water. The stupor continued, the paresis became more marked, the spasticity was replaced by flaccidity and the neck rigidity increased. A second lumbar puncture yielded xanthochromic fluid. The blood chemistry at this time was normal. The blood urea nitrogen rose to 54 mg. per cent, and the patient died on the following day.

*Anatomic Diagnosis:* Generalized arteriosclerosis including the nervous system, kidney and heart; hypertrophy and dilatation of the heart; bronchopneumonia; cholelithiasis.

*Autopsy of the Nervous System:* There were two large hemorrhages in the right temporal lobe; these extended into the parietal and occipital regions (figure 5 A). Other small areas of destruction were found throughout.

*Microscopic Examination:* An extensive area of devastation of both white and gray matter, punctate hemorrhages and pronounced proliferation of small arterioles and capillaries were noted in the right island of Reil. Adjacent areas showed moderate dropping out of nerve cells, ischemic cell changes, a similar but less marked proliferation of the vessels and perivascular gliosis. The small arterioles were thickened and showed extensive hyalinization, hyperplasia of the endothelium, narrowing of the lumen and adventitial proliferation (figures 5 B and C). Reduplication of the elastic lamina of the small thickened vessels was clearly brought out in the resorcin-fuchsin preparation. The adventitial spaces contained compound granular corpuscles. Similar but less marked changes were also noted in the frontal, parietal and occipital convolutions.

*Comment:* The cerebral changes in this, as in the other instances, were diffuse. The patient had suffered from headaches for eight years. For four years she had experienced attacks of numbness and blurring of vision. The abdominal pain and vomiting may have been cerebral in origin or may have been caused by the cholecystitis and cholelithiasis. The cerebral hemorrhage was a terminal event.

*Case 6.* F. L., a woman, aged 42, was admitted to this hospital on March 25, 1930, complaining of severe frontal headaches, dizziness, occasional attacks of epistaxis, easy fatigue, dyspnea on exertion and palpitation of the heart for the past four years. In January 1930, on awakening, she found her left side paralyzed.

*Physical Examination:* Examination revealed a large heart, an enlarged liver, some fluid at the base of the right pleural cavity and a blood pressure of 240 systolic and 140 diastolic. There was a residual hemiplegia on the left side.

*Laboratory Data:* The blood urea nitrogen was 14.9 mg. per cent. The urine contained 2 plus albumin and the specific gravity was 1.016.

*Course:* On the day after admission, the patient suddenly became comatose and showed signs of paralysis of the right side of the body. She remained in coma and died the next day.

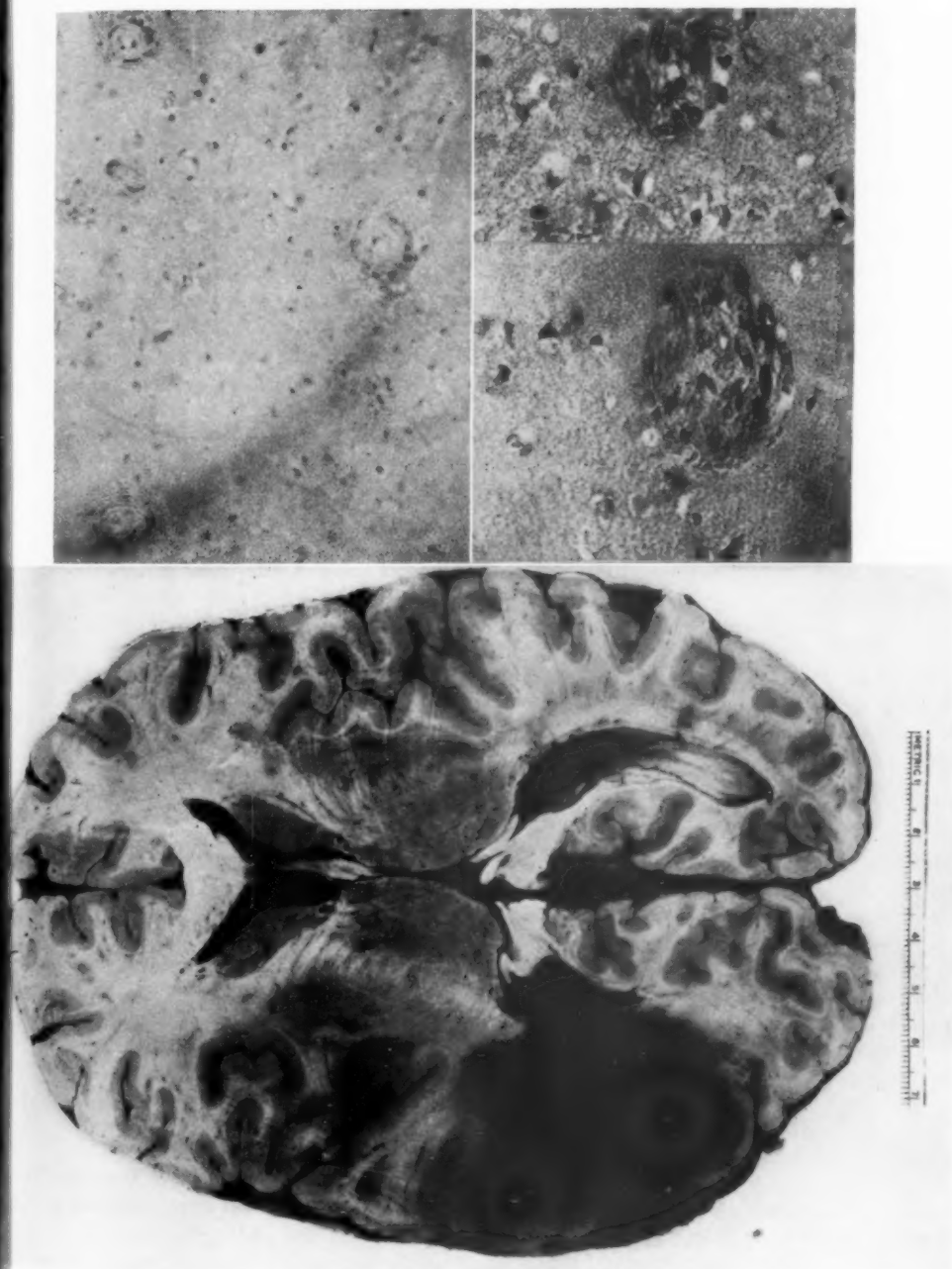


FIG. 5 A. (Case 5.) *Left.* Extensive hemorrhage in the right temporal and inferior parietal convolutions and numerous areas of destruction throughout.  
 FIG. 5 B. (Case 5.) *Upper right.* Hyalinization and endothelial proliferation of the small vessels with narrowing of the lumen. Cresyl violet  $\times 100$ .  
 FIG. 5 C. (Case 5.) *Lower right.* Proliferation of the adventitia of the cortical vessels. Hematoxylin-eosin  $\times 200$ .

*Anatomic Diagnosis:* Generalized arteriosclerosis including the nervous system, kidney and heart; cardiac hypertrophy and dilatation.

*Autopsy of the Nervous System:* The vessels at the base of the brain were markedly sclerotic. There were two hemorrhages in both hemispheres involving the internal capsules. The hemorrhage on the left was smaller than on the right, was more recent in origin, and extended into the parietal lobe. The hemorrhage on the right was organized.

*Microscopic Examination:* Sections from various cortical regions showed small areas of devastation and thickening of the walls of the small arterioles with narrowing of their lumina. In the resorcin-fuchsin preparation, the muscularis of the small arterioles showed the greatest hypertrophy. There was reduplication of the elastic lamina. The perivascular spaces were moderately dilated. A moderate loss of nerve cells in the cortical tissue, glia cells and axis cylinders in the white matter was noted around these sclerotic vessels. The normal arrangement of the cyto-architectural layers was lost.

*Comment:* In this instance the associated renal, cardiac and cerebral involvement was evident. In addition to the cerebral hemorrhages there were other diffuse lesions in the nervous system directly due to deficient circulation as a result of the changes in the walls of the arterioles and capillaries.

*Case 7.* R. G., a woman, aged 50, was admitted to this hospital on March 22, 1932. In 1928 the patient sustained a minor injury to her left hand which was immediately followed by a generalized convulsion lasting five minutes and unconsciousness. Soon there developed paralysis of the left side from which she recovered completely in six weeks. In December 1929, she became dizzy and fell, striking the back of her head. Two weeks later, occipital headache and nausea and stupor for about 2½ days set in. Upon regaining consciousness she was irrational and showed impairment of memory and judgment. The blood pressure at that time varied between 190-210 systolic and 110-140 diastolic. The left disc margin was blurred. In 1930 following some excitement, she had loss of memory for several weeks. On February 21, 1932, upon awakening, she experienced a weakness of the left side of the body and diplopia.

*Physical Examination:* Examination revealed an enlarged heart, a blood pressure of 210 systolic and 150 diastolic, hyperemia of the left disc, edema of the retina and a few small hemorrhages in the right fundus.

*Neurological Examination:* Examination revealed a left flaccid hemiparesis with exaggerated deep reflexes and positive Hoffmann and Babinski signs; intention tremor in left upper and lower extremities with asynergia; myoclonic movements of the eyes, soft palate, perioral muscles, tongue and lower jaw; a constant horizontal and rotary nystagmus; weakness of the right lateral rectus muscle, impairment of upward gaze and conjugate deviation to the left and a right supranuclear facial weakness.

*Laboratory Data:* The specific gravity of the urine varied between 1.012 and 1.016. A trace of albumin was present. The blood chemistry was normal and the Wassermann reaction of the blood was negative.

*Course:* Later the patient became mentally confused, had difficulty in swallowing, experienced choking sensations, urinary incontinence, emotional instability with outbursts of weeping and definite episodes of mental defect and disorientation. The neurological status was unchanged except for the addition of a right hemiplegia with positive signs of pyramidal tract involvement, dysarthria, pseudo-bulbar speech, impaired pain and temperature sensibility on the left side and a poor response of the left pupil to light. On December 8, 1932, she became unconscious, developed a flaccid paralysis of all extremities, signs of pneumonia and she died on December 13.

*Anatomic Diagnosis:* Generalized arteriosclerosis involving brain, kidney and heart; hypertrophy and dilatation of the heart; lobar pneumonia (right).

*Autopsy of the Nervous System:* The vessels at the base showed marked arteriosclerosis. There were areas of softening involving the first and second right orbital convolutions, the right caudate, the right centrum ovale, the right external nucleus of the thalamus (figure 6 A) and the pons near the right sixth nerve nucleus. Small foci of softening were found throughout the central nervous system. There was a fresh hemorrhage involving the left caudate, thalamus and internal capsule (figure 6 B).

*Microscopic Examination:* The vessels showed arteriosclerotic and endarteritic changes. In sections through the aqueduct, there were numerous thickened hyalinized vessels with little involvement of surrounding neural tissue. The small arterioles in the pons showed marked thickening of the intima and a pronounced glial reaction about them (figure 6 C). Numerous glia nodules were noted throughout, especially in the white matter of the cerebellum. The nerve cells of the various involved areas showed all types of pathologic changes.

*Comment:* The neurologic symptoms and signs are amply accounted for by the diffuse cerebrovascular disease. The brain in this case obviously bore the brunt of the changes secondary to hypertensive arteriolar disease.

## DISCUSSION

The original concept that the so-called Bright's disease associated with hypertension was essentially a disease of the kidneys was first questioned by Gull and Sutton<sup>2</sup> in 1872, who showed that arteriolosclerosis was not confined to the arterioles of the kidneys. Through the investigations of Jores,<sup>3</sup> Munzer,<sup>4</sup> Evans<sup>5</sup> and others, this fact was partially confirmed. Fishberg<sup>6</sup> in 1925 studied the anatomic findings in essential hypertension and reported that, although the kidney is most involved, other organs were also affected. The cerebral arterioles, he found, were diseased in 19 per cent of the cases. Branch and Linder<sup>7</sup> in 1926, Keith, Wagener and Kernohan<sup>8</sup> in 1928 and Kernohan, Anderson and Keith<sup>9</sup> in 1929 emphasized the diffuse disturbance in the arterial tree caused by hypertension.

The work of Volhard and Fahr,<sup>10</sup> Fahr,<sup>11</sup> Janeway,<sup>12</sup> Allbutt,<sup>13</sup> Ellis and Marrack,<sup>14</sup> and more recently of Wagener and Keith,<sup>15</sup> Fishberg,<sup>16</sup> Keith, Wagener and Kernohan,<sup>8</sup> and others, has led to a better understanding of the clinical course and associated pathology of cases of hypertension. It is now recognized that they generally terminate in one of three ways: (1) most commonly from cardiac failure, coronary sclerosis frequently complicated by slow or acute occlusion; (2) cerebral accident; and (3) least commonly, from renal insufficiency (10 per cent or less).

Although the clinical course of each type varies considerably, the pathologic changes are essentially quite similar. The secondary degenerative changes in the heart and kidney which give rise to well recognized clinical syndromes, also may take place in the brain causing a condition which has been called "cerebral vascular disease," "arteriosclerotic brain atrophy (Alzheimer)," "encephalomalacia" or "cerebral arteriosclerosis."

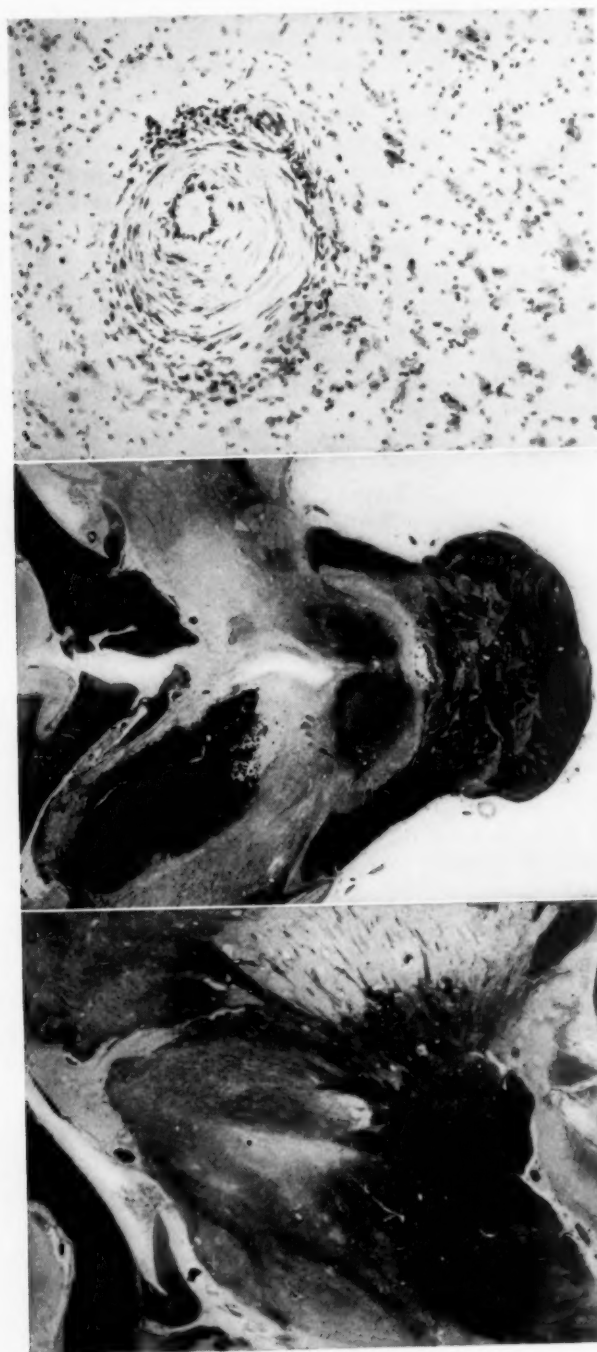


FIG. 6 A. (Case 7.) *Left.* Small areas of softening in the right lateral thalamic nucleus and internal capsule.  
 FIG. 6 B. (Case 7.) *Center.* Hemorrhage in the left thalamus.  
 FIG. 6 C. (Case 7.) *Right.* Thickening of vessel and perivascular gliosis. Cresyl violet  $\times 100$ .

Many of the clinical symptoms such as headaches, dizziness, dysesthesias, fleeting paralyses, transient aphasia, temporary or permanent personality changes and intellectual impairment are explained on the basis of the findings described in our cases.

An attempt was made to demonstrate that cerebral changes are a frequent accompaniment of cardiac and renal disease, during the course of essential hypertension. In our cases the brain was more extensively involved than the other organs. The diffuse areas of softening, the focal hemorrhages, the small focal areas of devastation, the disturbances in cyto-architectural arrangement, the dropping-out of ganglion cells, the degenerative nerve cell changes and the glia nodule formation were due to arteriolar changes. These are the indisputable marks of long-standing progressive lesions, many of which have their clinical counterparts, those in silent areas having none. The more obvious hemorrhages and thromboses of larger vessels are all secondary to the disease of the arteries produced by elevated blood pressure.

Clinically, the significant facts in this series showed that all the patients were comparatively young individuals, the average age being 38. Several cases in older persons were deliberately excluded to eliminate the complicating factors of senile arteriosclerotic encephalopathy. The average span of life following the onset of the symptoms was about five years. The first case lived the longest—13 years, and the fourth case lived for only 1½ years. Five out of the seven cases died of a terminal cerebral hemorrhage. The average systolic blood pressure was 210 and the average diastolic was 140. The patient who lived the longest had the lowest blood pressure.

The cases were all characterized clinically by a succession of neurological symptoms due to large and small cerebral vascular insults. Cardiac and renal symptoms were relatively inconspicuous and unimportant. The course was progressive; cerebral manifestations occurred before there was any clinical or laboratory evidence of renal or cardiac insufficiency. Death in most instances was ultimately the result of "cerebral failure."

Keith, Wagener and Kernohan<sup>8</sup> described a cerebral form of malignant hypertension, a characteristic feature of which was edema of the disc, often out of proportion to the other retinal changes. This condition which was present in all their cases was found in only three of our cases. None of the three cases ran a course radically different from the others or showed pathologic changes that would distinguish them from the remainder of the group. The pathologic changes in four brains they examined were similar to those found in our cases. Although Keith's classification appears to be legitimate, we believe that a regrouping is warranted, based not upon the presence or absence of a certain type of retinitis, but upon striking clinical and pathologic resemblances. In the absence of necrotizing arteriolitis and renal insufficiency, the diagnosis of "malignant phase of essential hypertension," as reported by Fishberg,<sup>16</sup> and Klemperer and Otani,<sup>17</sup> cannot be applied to our cases.

The histopathologic changes previously described by Bodechtel<sup>18</sup> and Hechst<sup>19</sup> in uremia are similar to those observed in our cases and most likely were due to accompanying hypertensive vascular disease. Bodechtel<sup>18</sup> demonstrated small areas of devastation in the cortex, glia nodule formation and small areas of softening in uremia. Hechst<sup>19</sup> noted in cases of uremia hyalin degeneration of the media of the small vessels of the brain, areas of softening, chronic cell changes and glia nodules. Neubürger,<sup>20</sup> who described diffuse neural changes, mentioned the difficulty in differentiating between hypertensive, arteriosclerotic and embolic lesions. He believed, however, that the presence of red infarcts, severe arteriolar damage and the ischemic cell changes in Ammon's horn are characteristic of hypertensive involvement.

"Chronic hypertensive encephalopathy" is the appropriate term for cases with progressive and diffuse cerebral changes and focal signs caused by arteriolar disease, secondary to hypertension.

#### SUMMARY AND CONCLUSIONS

1. Hypertension is associated with generalized arteriolar changes.
2. In some instances, the cerebral vessels are primarily affected, resulting in widespread neural involvement, with relative sparing of the heart and kidney.
3. Clinically these cases were characterized by diffuse neurological signs and symptoms and by a progressive down-hill course. Death resulted from cerebral failure, usually from a terminal hemorrhage.
4. The term "chronic hypertensive encephalopathy" is proposed to describe these cases.

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# HEMOLYTIC JAUNDICE AND MACROCYTIC HEMOLYTIC ANEMIA: CERTAIN OBSERVATIONS IN A SERIES OF 35 CASES \*

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DURING the past six years opportunity has been afforded to study 35 patients † exhibiting evidence of hemolytic anemia or jaundice. These cases were divided as follows:

1. Microcytic (familial or congenital) type ..... 20
2. Macrocytic (secondary or acquired) type ..... 15
  - a. With liver disease ..... 8
  - b. With Hodgkin's disease ..... 3
  - c. With leukemia ..... 2
  - d. With chronic bleeding into ovarian cyst 1
  - e. With hyperthyroidism ..... 1

It will be noted that the cases in the second group were in all instances associated with other disease. The existence of a primary form of acquired hemolytic jaundice has been questioned more and more in recent years. There is little doubt that the vast majority, if not all of the cases of primary hemolytic jaundice are of the familial or congenital type. In the earlier literature (Eppinger<sup>1</sup>), patients whose jaundice appeared first in adult life, and in whose family no other members were icteric, were often wrongly classified as instances of the acquired type. This was true even though fragile microcytes were demonstrated. One of the cases of familial hemolytic jaundice in the present series illustrates how easily such a mistake might be made. This patient, a male 22 years of age, had first become jaundiced at 19. Since then there had been varying degrees of jaundice and anemia. The spleen was markedly enlarged. Deeply staining microcytes were numerous in the stained smear of his blood. In hypotonic saline hemolysis of the erythrocytes began at 0.68 per cent and was complete at 0.42 per cent. (Control: H<sub>1</sub> 0.44 per cent, H<sub>2</sub> 0.34 per cent.) Careful questioning of the

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† In somewhat more than a year since this paper was written, 13 additional instances of hemolytic anemia have been studied. Seven of these were typical cases of the familial, microcytic type, four were in association with leukemia, one was noted in a patient with cirrhosis of the liver, and another in a case of probable diffuse splenic fibrosis, or Banti's disease. The feces urobilinogen and reticulocyte percentage were elevated in varying degree in all of these cases. Of the four cases of leukemia, the anemia was macrocytic in three, as judged by mean corpuscular volume and mean diameter of the erythrocytes. Measurements were not recorded in the fourth. It is of interest that two of these four cases were instances of subleukemic, splenic reticuloendotheliosis. Outspoken macrocytosis was present in the two patients with cirrhosis, and with Banti's disease.

relatives failed to elicit a history of jaundice or splenic enlargement in any. The mother, father and six brothers were examined and none were found to exhibit jaundice or splenomegaly. Two of the members of the immediate family were examined as to fragility of erythrocytes. The resistance of one of the brother's erythrocytes to hypotonic saline was definitely diminished:  $H_1$  0.56 per cent,  $H_2$  0.42 per cent. The values for the father were normal:  $H_1$  0.44 per cent,  $H_2$  0.32 per cent. From this it is evident that the underlying affection was familial, although only the patient presented obvious manifestations, and these failed to appear until early adult life.

In two of the cases of macrocytic type, the hemolytic anemia persisted after removal of the associated pathologic conditions, which in one was a bleeding ovarian cyst, and in the other a diffuse hyperplasia of the thyroid with hyperthyroidism. Some of the features in the first of these two cases have already been described,<sup>2, 30</sup> but inasmuch as this is perhaps the most important case of the series, a more detailed report will now be given.

#### CASE REPORT

The patient was a female, 19 years of age. She had always been healthy until the age of 17 when she first noticed mild jaundice. This had frequently recurred, ushered in by slight chilly sensations and headache, and accompanied later by a dull diffuse abdominal distress. There was no familial history of jaundice. Examination revealed mild jaundice and obvious anemia. The spleen was not palpable, either at the time of the first, or of many subsequent examinations. A mass was palpable in the left lower quadrant of the abdomen; on bimanual examination, this was evidently in the region of the left ovary; the mass was smooth, firm and appeared to be cystic. Examination of the blood revealed: Hemoglobin 32 per cent, erythrocytes 1,150,000, leukocytes 6900, 76 per cent neutrophils. Stained smears exhibited marked anisocytosis of the erythrocytes with predominance of macrocytes; the average cell diameter was 8.8 micra. (This value was obtained with the Bock apparatus,<sup>4</sup> the normal for which in this vicinity is 7.6 to 8.0 micra.) The reticulocytes were 15 per cent. The resistance of erythrocytes to hypotonic saline was:  $H_1$  0.38 per cent,  $H_2$  0.32 per cent. (Control:  $H_1$  0.38 per cent,  $H_2$  0.30 per cent.) Marked spontaneous autohemagglutination was exhibited by the patient's blood. This was definitely related to temperature, the agglutination appearing first about 30° C., disappearing when the blood was warmed to 37° C. The agglutinins resided in the plasma and could be removed completely by repeated subjection of the same sample of plasma to washed erythrocytes, either those of the patient, or of another group O individual. It was possible to group the patient's blood only after dilution of at least 1:20 in physiological saline. The question arose as to whether autohemagglutination had interfered with measurement of the resistance of the erythrocytes to hypotonic saline. This possibility was excluded by carrying out the fragility test at a temperature of 37° C. Even with this precaution, no deviation from the normal was found. The icterus index at time of admission was 42; later, however, even with increasing anemia, it usually ranged from 12 to 20. The Van den Bergh reaction was positive and of the indirect type. The urine contained no bilirubin and but relatively small amounts of urobilinogen, varying from 2.4 to 9.8 mg. per day. The feces urobilinogen was markedly increased, ranging from 986 to 1106 mg. per day.

All of these findings indicated increased hemoglobin destruction, but since it was conceivable that internal bleeding might be responsible, an exploration of the abdomen with reference to the pelvic mass was decided upon. The patient was trans-

fused repeatedly and a large ovarian cyst containing 800 c.c. of dark brown fluid was removed from the left side of the pelvis. This fluid contained much hematin, but no bilirubin. The operation, however, failed to bring improvement; shortly afterwards the hemoglobin declined from 59 per cent, to which it had risen as a result of preoperative transfusions, to 39 per cent and then more gradually fell to a low of 23 per cent. Transfusions were again resorted to but were now often productive of severe febrile reactions and at times obviously initiated "hemolytic crises." The usual course of events was that an immediate rise of several points in hemoglobin level would occur, but within 24 hours the patient would experience increase in fever, nausea and jaundice, and the hemoglobin would rapidly decline. This was true following a direct transfusion as well as after citrated blood. The rather frequent untoward results of blood transfusions in hemolytic jaundice have been commented upon repeatedly in the recent literature.<sup>5, 6, 7, 8</sup> In two other cases of the present series blood transfusion was followed by a temporary increase in jaundice and a rather rapid decrease in hemoglobin. In the case just described the hemoglobin had declined to 28 per cent in spite of several transfusions. This was after an interval of 20 days subsequent to removal of the cyst. It was now decided to discontinue transfusions for a time in the hope that they might be tolerated better after a period of rest. During the next 10 days the hemoglobin declined further to 26 per cent; the reticulocytes were fluctuating between 10 and 17 per cent. At the end of this interval it was decided to transfuse the patient again and carry out splenectomy. Accordingly, transfusions of 500 c.c. of citrated blood were given, one each, on April 8, 9, and 11, 1935. Interestingly enough, these transfusions were attended by very little reaction. The hemoglobin had risen on April 11 to 51 per cent with 2,300,000 erythrocytes per cu. mm. Splenectomy was carried out by Dr. Owen Wangenstein. The spleen weighed but 440 gm.; microscopic study revealed marked congestion of the pulp, with rather narrow sinuses.

The immediate postoperative course was quite unlike that usually noted in cases of familial hemolytic jaundice. Instead of a progressive increase in hemoglobin and erythrocytes with a marked decline in urobilinogen excretion<sup>3c, 5</sup> the latter remained markedly elevated while the former steadily declined. This decline was associated with a marked drop in reticulocytes. All of these changes may be seen in the following table:

Date	Hemoglobin, Per cent	Erythrocytes, mill. per cu. mm.	Reticulocytes, Per cent
4-8-35.....			15.0
4-11.....	51	2.30	
Splenectomy			
4-15.....	51	2.70	0.3
4-16.....	48	2.21	0.6
4-17.....	49	2.38	1.8
4-18.....	46	2.28	3.6
4-19.....	46	2.20	4.8
4-20.....	40	2.07	8.6
4-22.....	48	2.63	22.2
4-24.....	49	2.59	21.6
4-26.....	54	2.66	16.8
4-29.....	57	3.02	12.2

From the above it will be seen that the anemia increased until the reticulocytes again became elevated. When these findings are compared with the urobilinogen excretion, it is evident that the patient suffered from another, although relatively mild, "hemolytic crisis," even after splenectomy. Fortunately, this was the last such episode. On April 25 the feces urobilinogen was found to be 1548 mg. per day, as con-

trasted with a normal range of 40 to 280 mg.<sup>3b</sup> By May 10, one month after splenectomy, the value had fallen to 429 mg. daily, still nearly twice the upper limit of normal; the icterus index at this time was 19. The very slow decline of the feces urobilinogen is quite dissimilar to the rapid decline usually observed following splenectomy in familial hemolytic jaundice.<sup>3c</sup> After May 15 the patient's condition improved steadily; by July 2 the icterus index had fallen to 10, and the feces urobilinogen to 203.6 mg. per day. On August 1 the hemoglobin had risen to 72 per cent and the erythrocytes to 3,180,000 per cu. mm. The patient was seen again at intervals, the last time in May, 1937. The hemoglobin was now 88 per cent, there was no icterus, and there had been no recurrence of symptoms. It is worthy of note that the autohemagglutination had now entirely disappeared although it persisted for several months after splenectomy.\*

The patient with hyperthyroidism and macrocytic hemolytic anemia was kept under observation for two months after subtotal thyroidectomy had been carried out. At this time the symptoms of hyperthyroidism had disappeared, the basal metabolic rate having declined from + 40 per cent prior to operation, to + 16 per cent. Nevertheless, the hemolytic anemia had persisted and the hemoglobin had fallen to 42 per cent. The feces urobilinogen remained constantly elevated, ranging from 500 to 1000 mg. per day. The patient returned to her home, refusing splenectomy. Several weeks later a report was received from her local physician that splenectomy had been carried out but that death, ascribed to pulmonary embolism, had occurred a number of days after operation.

Particular attention has been given to the first of these two cases because of its importance with reference to the question of acquired hemolytic jaundice. Regardless of the possibility that reabsorption of hematin from the hemorrhagic ovarian cyst may have stimulated blood destruction at the outset, it is quite clear that the condition of hemolytic anemia persisted to a dangerous degree long after removal of the cyst. The case must, therefore, be classified as an idiopathic one. As compared with familial hemolytic anemia, this case differed in three respects, which will now be considered in relation to the entire group of patients. These three respects are: (1) size of erythrocytes, (2) fragility of erythrocytes (resistance to hypotonic saline), (3) autohemagglutination. In the distinction of familial from acquired hemolytic anemia or jaundice, the first of these is unquestionably the most important.

#### SIZE OF ERYTHROCYTES

Of the 15 cases of acquired hemolytic anemia in the present series, all exhibited red blood cells at least slightly larger, and often much larger than the normal. Of the various diseases represented in this group, each has been previously noted to be associated at times with a macrocytic anemia. (Liver disease<sup>3a, 4, 9, 10</sup>; Hodgkin's disease and leukemia.<sup>3c, 11, 12</sup>) Of the 20

\* This patient was studied again on January 3, 1939. At this time the hemoglobin was 90 per cent, the erythrocytes 4,160,000 per cu. mm., the average diameter of the erythrocytes 7.8  $\mu$ , and the reticulocytes 2.2 per cent. There was no icterus and subjectively the patient was entirely normal.

cases of familial hemolytic anemia or jaundice, represented in the present series, all exhibited red blood cells which were smaller, on the average, than normal. With the Bock erythrocytometer the average diameter was found to range from 6.6 to 7.2  $\mu$ , whereas in the acquired group it was regularly more than 8.0  $\mu$ . Evidence of familial incidence was obtained from the history or from examination of the relatives in each of the 20 instances of the familial type. With one exception, the history was negative in this respect in the macrocytic group. In one of the cases of cirrhosis of the liver, which will be referred to again in the following, the patient's brother was said to have died of "pernicious anemia."

#### RESISTANCE OF ERYTHROCYTES TO HYPOTONIC SALINE

Increased fragility of erythrocytes was not strictly limited to the microcytic (familial) group of cases. Two of the cases which were classified as macrocytic hemolytic anemia in association with liver disease, exhibited decreased resistance of the erythrocytes to hypotonic saline. In one of these, a female aged 30, hemolysis began at 0.64 per cent ( $H_1$ ) and was complete at 0.42 per cent ( $H_2$ ), whereas the control was:  $H_1$  0.52 per cent,  $H_2$  0.38 per cent. In the other, a female aged 68, the abnormality was less striking:  $H_1$  0.46 per cent,  $H_2$  0.40 per cent; control  $H_1$  0.40 per cent,  $H_2$  0.34 per cent. It should be emphasized that both of these patients were suffering from moderately severe anemia of macrocytic type; the average red blood cell diameter in the first was 8.35  $\mu$ , and in the second 8.1  $\mu$ . From this it is clear that increased fragility may at times occur in anemias other than those characterized by the presence of spherical microcytes. On the other hand, the present series of cases of familial hemolytic jaundice exhibited increased fragility without exception. In Gänsslen's large series<sup>13</sup> a few exceptions were noted. Haden<sup>14a</sup> believes that the microcytes of familial hemolytic jaundice are more fragile because of their spherical shape; in the laking of normal erythrocytes by gradual addition of distilled water, he found that the normally biconcave discs first tend to become spherical and then undergo hemolysis as the solution becomes more hypotonic. This observation, coupled with the likelihood that the spherical microcyte is the chief inherited fault in the familial form of the disease, makes it difficult to conceive of cases which would not exhibit increased fragility. Conversely, one would not expect to observe increased fragility in macrocytic anemias, such as in the two which have just been mentioned. The question naturally arises as to whether the thickness of the macrocytes in these cases is increased to such a degree that increased fragility might be expected. Data from the second case yield some information in this regard:

Mean corpuscular volume: 133 cu. $\mu$	Normal
Average diameter: 8.1 $\mu$	80-94 cu. $\mu$ (Wintrobe, 15)
Cell thickness: $\frac{\text{vol}}{\pi r^2}$ (v. Boros, 16) = 2.6 $\mu$	7.6-7.8 $\mu$
	1.2-2.0 $\mu$

From these findings it is evident that although the cells were slightly thicker than normal in proportion to their increased diameter, they were not spherical. At the time the above determinations were made the resistance of the erythrocytes to hypotonic saline was determined again, with the following result:  $H_1$  0.56 per cent,  $H_2$  0.42 per cent; control,  $H_1$  0.42 per cent,  $H_2$  0.34 per cent. (Further studies of this patient are described on page 1793.) This result is in accord with Vaughan's recent report<sup>14b</sup> that increased fragility invariably persisted after splenectomy but that spherocytosis disappeared in about 50 per cent of cases, a finding which indicates that some abnormality other than simple spherocytosis may be responsible for the increased fragility.

According to recent studies by Dameshek and Schwartz,<sup>29, 30</sup> the possibility would have to be considered that macrocytosis such as in the above instance is related simply to an increased percentage of reticulocytes, and that there might still exist an underlying spherocytosis to account for the moderately increased fragility. Dameshek and Schwartz<sup>30</sup> believe that an increased number of reticulocytes produce a "pseudomacrocytic" anemia, but that the various hemolytic anemias are generally related to the formation of spherocytes, probably as a response to the presence of isohemolysins. Although the writer's observations do not touch upon the latter question, they do reveal clearly that the mean erythrocyte diameter (M.C.D.) is not closely correlated with the reticulocyte percentage, in different instances of hemolytic anemia. This is illustrated by the following data:

	M.C.D.	M.C.V.	Retic. per cent	$H_1$
Case 1. Familial hemolytic jaundice.....	7.0 $\mu$ *	87.0	15.2	<0.7
Case 2. Familial hemolytic jaundice.....	6.9 $\mu$ *	104.0	27.6	<0.7
Case 3. Familial hemolytic jaundice.....	7.3 $\mu$ *	115.0	12.0	<0.7
Case 4. Familial hemolytic jaundice.....	6.9 $\mu$ † 7.0 $\mu$ *	77.0	14.0	<0.7
Case 5. Reticuloendotheliosis; macrocytic hemolytic anemia.....	8.25*	111.0	4.6-7.0	0.54 (control 0.54)
Case 6. Splenic anemia; probable diffuse splenic fibrosis; macrocytic hemolytic anemia...	8.2	119.5	4.5	0.44 (control 0.48)
Case 7. Cirrhosis of the liver; mild macrocytic hemolytic anemia.....	8.4*	100.0	3.6	0.44 (control 0.48)
Case 8. Hemorrhagic ovarian cyst; severe macrocytic hemolytic anemia.....	8.8†	—	15.0	0.38 (control 0.38)
(Case described in foregoing)				

\* Bock erythrocytometer.

† Pijper halometer (C. Zeiss & Co.).

$H_1$  = concentration of salt solution in which hemolysis commenced in the fragility test.

The data given by Dameshek and Schwartz<sup>29</sup> for three cases of acute hemolytic anemia, also fail to reveal correlation between the M.C.D. and reticulocyte percentage. The values are as follows:

	M.C.V.	M.C.D.	Retic. per cent
Case 1		7.55	12.0
Case 2	125	7.44	20.8
Case 3	80	6.4	20.6

(The M.C.D. was determined in these instances by the Price-Jones curve.)

Thus it is clear that varying reticulocytosis does not explain the marked difference in M.C.D. noted between the cases of familial hemolytic anemia, and those that have been classified here as macrocytic hemolytic anemia. It is believed that there are many instances of the latter type, differing fundamentally from the familial or microcytic form, and that the term "pseudo-macrocytic" is not appropriate for these cases. Although reticulocytes are unquestionably larger than mature erythrocytes, the macrocytic tendency effected by them is not sufficiently great to interfere in the distinction of the two forms of hemolytic anemia, as described in the foregoing.

#### RELATIONSHIP OF JAUNDICE AND ANEMIA

In considering the pathogenesis of jaundice and anemia, it is quite evident that three factors are of importance, at least insofar as the familial form of the disease is concerned. These are: (1) the more fragile erythrocytes, (2) hypersplenism, and (3) bilirubin excretory function of the liver. Of the three, it is clear that the second is of prime importance. Under normal conditions, certain animals have small erythrocytes which behave toward hypotonic saline in quite the same fashion as do the spherical microcytes of hemolytic jaundice patients. This is most marked in the goat,<sup>14a</sup> and yet the goat is not afflicted with jaundice, anemia, or splenic enlargement. Quite similarly, certain members of hemolytic jaundice families may go through life without developing any of these manifestations, although, as noted at the outset, they will often be found to have the characteristic spherocytes.

Although there can be no doubt that hypersplenism is responsible for excessive wastage of erythrocytes with resultant over-production of bilirubin, a comparison of the degree of jaundice and anemia in the present series of cases reveals clearly that these are not correlated phenomena and that the bilirubin excretory function of the liver must be regarded as the most important, probably the sole factor in determining the presence or absence of jaundice. Except during hemolytic "crises" jaundice and anemia are not proportional in degree; in fact, a distinct tendency toward an inverse relationship exists. In this regard it seems particularly noteworthy that the two extremes of jaundice or anemia in this series exhibited the most anemia and the least jaundice and vice versa. Thus, one case was that of a boy of 16 who came to the hospital because of profound anemia, but who was not, and never had been jaundiced. The icterus index was 8, the hemoglobin 20 per cent (17 gm. per 100 c.c. = 100 per cent); splenomegaly and spherical microcytes were found, and the feces contained 792.9 mg. of urobilinogen per day. Complete recovery from the anemia took place after splenectomy. In striking contrast to this case was a boy of 18

who presented himself because of jaundice without anemia and who was unwilling to consider splenectomy because he had never been sufficiently sick. The icterus index in this case varied between 45 and 92, while the hemoglobin ranged between 80 and 90 per cent. This patient, of course, typifies Chauffard's characterization,<sup>17</sup> "more jaundiced than sick." The contrast between these cases strongly suggests that relative liver dysfunction is somewhat of an asset in familial hemolytic icterus. Study of the urine urobilinogen in these patients offers further evidence of the more sluggish liver function in the cases whose jaundice is most marked. In general, much larger amounts of urobilinogen were found in the urine of patients with relatively little anemia, but much jaundice. On the contrary the amounts were normal or but slightly increased in those cases with much anemia and little or no jaundice. It may be emphasized that, contrary to common belief, urobilinogen is often not increased in the urine in patients showing even marked increase of blood destruction. The urobilinogen was not increased in the urine of the patient mentioned above, who suffered from severe (spherocytic) hemolytic anemia, without jaundice.

It should be pointed out that hemolytic "crises" usually constitute an exception to this tendency to an inverse relationship between jaundice and anemia. During these periods a parallel increase of jaundice and anemia is often seen. This is usually followed by some decline in the degree of jaundice together with a rapid increase in the hemoglobin and erythrocytes. For example, in one of the cases in the present series the hemoglobin fell from 54 to 45 per cent during three days of a mild hemolytic "crisis"; the icterus index rose from 20 to 32. In the next 13 days the hemoglobin rose spontaneously to 78 per cent, and the icterus index returned to 20.

#### AUTOHEMAGGLUTINATION

Widal and his associates<sup>18</sup> were the first to regard autohemagglutination as a distinguishing feature of acquired hemolytic jaundice. Although the experience in the present series appears to bear this out, inasmuch as it was observed twice in the acquired group and not at all in the familial cases, the phenomenon is, nevertheless, of doubtful reliability so far as this distinction is concerned. Thus, Masters and his associates<sup>19</sup> noted autohemagglutination in two cases of hemolytic jaundice in the same family. Both exhibited microcytes and increased fragility. Tileston<sup>20</sup> states that autoagglutination is rare except in hemolytic jaundice and that there may be a causal relationship, but a survey of the literature makes it clear that increased blood destruction and autoagglutination are by no means strictly correlated. In the above described case of acquired hemolytic jaundice in which increased hemolysis persisted for some time after splenectomy, the autohemagglutination was noted for an even longer period, in fact it was still present two months after the signs of increased blood destruction had disappeared. The phenomenon has been observed in a case of bronchopneumonia without anemia,<sup>21</sup> and in a pregnant woman with severe anemia

due to bleeding hemorrhoids.<sup>22</sup> The writer has recently noted its occurrence in a case of polycythemia vera. Here, however, it was not as marked as in the cases of hemolytic jaundice. In multiple myeloma, Reimann<sup>23</sup> was the first to observe autoagglutination. It appears to occur rather regularly in this disease and has been noted in each of the last five cases seen in the University of Minnesota Hospital. This form of autoagglutination, however, depends upon marked rouleau formation and differs further from that seen in hemolytic jaundice in that it is not affected by temperature; the agglutination of erythrocytes is not reversible at 37° C. Its occurrence in vivo is evidently prevented simply by virtue of the rate of blood flow; thus, in cases of multiple myeloma whose blood exhibited autoagglutination, Foord<sup>24</sup> was able to produce clumping of the erythrocytes in the retinal vessels simply by adequate pressure on the eyeball. As demonstrated first by Reimann,<sup>23</sup> the rouleau formation of multiple myeloma is on the basis of hyperglobulinemia, whereas the autohemagglutination due to "cold" agglutinins may occur to a marked extent when there is no abnormality in the plasma proteins. Thus, in the case of acquired hemolytic jaundice in this series, in which the autohemagglutination was the most marked, the plasma proteins were: Fibrinogen, 0.41 per cent, euglobulin 0.29 per cent, pseudoglobulin 1.55 per cent, albumin 3.92 per cent, total 6.17 per cent.

#### RELATIONSHIP OF THE SPLEEN TO THE NUMBER OF CIRCULATING ERYTHROCYTES

Barcroft's studies<sup>25</sup> revealed that the spleen in several species of animals serves as a reservoir for erythrocytes. To what extent his conclusions can be applied to the human spleen is not certain, but it is probable that temporary increases of erythrocytes produced by epinephrine are secondary to splenic contraction. It was possible recently to observe the effect of epinephrine on the spleen of a patient (not having hemolytic jaundice or anemia) who had previously been given thorotrast,\* and at the same time to note the variations in the number of circulating erythrocytes. By approximate estimation of the volume of the spleen, a definite reduction in size was estab-

Time in minutes after administration of 1 c.c. 1/1000 epinephrine subcutaneously	Erythrocytes in millions per cu. mm.	Estimated volume of spleen by X-ray. (100% = volume before administration of epinephrine)
0	3.57	100%
5		50%
10		50%
15	4.08	50%
20		70%
30	4.11	90%
40		100%
45	3.85	
60	3.64	

\* Unpublished study with Dr. Leo Rigler.

lished, and, as noted below, this was shortly followed by a temporary, significant increase in the number of circulating erythrocytes.

Doan and his associates<sup>8</sup> have called attention to the marked increase in hemoglobin and erythrocytes commonly observed within the first few hours after splenectomy. They ascribe this increase in part to the epinephrine administered preoperatively and in part to the elimination of inhibitory influences affecting the bone marrow. Data obtained in certain of the present series of cases of hemolytic anemia indicate that the preoperative effect of adrenalin is of itself quite adequate to explain this increase. The following observations were made as shown in table on page 1780.

In the above instance it was clear that epinephrine produced a rapid and considerable increase in hemoglobin and erythrocytes; after splenectomy this effect could not be reproduced.

In the following case, the data again suggest that excitement or emotional factors alone may suffice to bring about a significant elevation of hemoglobin and erythrocytes.

Date	Hemoglobin, per cent	Erythrocytes in mill. per cu. mm.
4-11 11:45 a.m.	51	2.30
1:15 p.m.	60	2.93
2:00-2:50 p.m.	Splenectomy accompanied by blood transfusions.	{ Patient nervous and apprehensive before preoperative sedation.
3:00 p.m.	56	
5:00 p.m.	62	3.13
10:00 p.m.	61	3.17
4-12 9:00 a.m.	54	2.77

The above observations indicate that the effect of epinephrine with consequent splenic contraction and liberation of erythrocytes to the circulation is quite adequate to account for the immediate postoperative increase in hemoglobin and erythrocytes.\* Although it is probable that some individual variation exists, the present observations indicate that, in carrying out splenectomy, epinephrine should be administered about one-half hour prior to clamping the splenic pedicle, if a maximum autotransfusion is to be obtained.

#### LIVER DISEASE AND HEMOLYTIC ANEMIA OR JAUNDICE

Increased blood destruction in association with liver disease has been referred to in some detail in a previous communication.<sup>30</sup> In the present series of cases, eight were included in whom this combination was observed. Seven of these were cases of cirrhosis of the liver, one was a patient with a severe, prolonged "catarrhal" jaundice. The latter was case 71 in the writer's previous report,<sup>30</sup> while six of the seven cases of cirrhosis were

\* Since this was written, similar studies of the effect of epinephrine have been carried out in four additional cases of familial hemolytic jaundice. In each instance the results were essentially the same as are given above.

	Date	Hemoglobin per cent	Erythrocytes in mill. per cu. mm.	
(Case 1)	6-13	56	2.0	Patient angry and disturbed because she was told that splenectomy had been postponed.
	6-15	72	3.5	
	6-16 8:30 a.m.	64	2.7	
	8:35 a.m.	0.5 c.c. 1/1000 epinephrine		
	6-16 9:30 a.m.	73	3.5	
(Case 2)	8-6	62	3.3	
	8-7	63	3.3	
	8-8	60	3.0	
	8-9 10:00 a.m.	67	3.5	
	10:30 a.m.	67	3.49	
	11:00 a.m.	65	3.23	
	11:05 a.m.	0.5 c.c. 1/1000 epinephrine		
	11:35 a.m.	81	4.18	
	12:05 p.m.	75	3.88	
	12:35 p.m.	71	3.6	
	1:35 p.m.	60	2.96	
	2:35 p.m.	66	3.52	
	5:35 p.m.	65	3.32	
	8-10	66	3.37	
	8-11	Splenectomy—uneventful recovery (epinephrine given just prior to operation)		
	8-23 9:00 a.m.	75	4.8	
	9:30 a.m.	74	5.2	
	10:00 a.m.	74	5.3	
	10:10 a.m.	0.5 c.c. 1/1000 epinephrine		
	10:40 a.m.	75	5.28	
	11:10 a.m.	74	4.32	
	11:40 a.m.	70	5.08	
	12:40 a.m.	70	4.2	
	1:40 p.m.	70	4.08	
	4:40 p.m.	71	4.8	
(Case 3)	2-25 10:00 a.m.	47	2.51	
	10:00 a.m.	0.5 c.c. 1/1000 epinephrine		
	10:15 a.m.	53	3.26	
	10:30 a.m.	57	3.71	
	10:45 a.m.		3.70	
	11:30 a.m.	59	3.60	
	2-28 10:00 a.m.	50	3.30	
	10:00 a.m.	0.5 c.c. 1/1000 epinephrine		
	10:15 a.m.	63	3.35	
	10:30 a.m.	63	3.55	
	10:45 a.m.	62	4.35	
	11:00 a.m.	59	3.28	
	11:30 a.m.	52	3.00	
	3-8	Splenectomy—uneventful recovery (epinephrine given just prior to operation)		
	3-16 10:00 a.m.	84	6.34	
	10:00 a.m.	0.5 c.c. epinephrine		
	10:15 a.m.	86	6.22	
	10:30 a.m.	86	6.46	
	10:45 a.m.	88	6.75	
	11:00 a.m.	84	6.42	
	11:30 a.m.	84	6.22	

numbers 70, 72, 73, 74, 75, and 76. The seventh has been observed subsequently; in this case there was a slight increase in the rate of blood destruction with mild jaundice, but without anemia. The patient, a male 68 years

of age, was found to have ascites, enlarged spleen and liver. The icterus index ranged from 13 to 16. The hemoglobin was 91 per cent (100 per cent = 17 gm. per 100 c.c.) The feces urobilinogen was 274 mg. per day, the amount in the urine ranging from 19 to 45 mg. daily (normal 0-4), so that the total urobilinogen excretion was definitely in excess of the upper limit of normal, which was found to be 280 mg. per day.<sup>3b</sup> In the earlier study, data were given for each of the cases of the above numbers, so that it is unnecessary to repeat this at present. Case 74 in the previous series has been studied on two subsequent occasions, and the later findings \* require further mention. This patient had the most severe anemia of any in the group of eight. In 1933 a prolonged "hemolytic crisis" occurred from which the patient eventually recovered and following which she remained fairly well until 1937. A moderate amount of ascites was noted in 1934. About this time the patient left the vicinity and was not seen again until the spring of 1937. She was now 71 years of age. Mild icterus and anemia had recurred; the hemoglobin was 60 per cent, and the icterus index 18. Splenectomy was recommended but refused. The patient left the hospital and was not seen again until August 13, 1937. At this time the anemia had markedly increased; the hemoglobin was 35 per cent, icterus index 43, feces urobilinogen 1660 mg. per day, urine urobilinogen 9.3 mg. per day. From 8-13 to 8-22 the patient was observed in the hospital and received occasional blood transfusions without appreciable benefit. The hemoglobin level gradually declined to 25 per cent. Splenectomy was decided upon, and accordingly, 3000 c.c. of citrated blood were given by drip transfusion during a 48 hour period. Just prior to operation the hemoglobin was 53 per cent, and the patient's condition appeared distinctly improved. Splenectomy was carried out by Dr. W. T. Peyton. The spleen weighed 880 gm. The liver was enlarged and quite cirrhotic. The peritoneal cavity contained at least a liter of clear, yellow fluid. For the first two post-operative days the patient's condition was good. On the third day, however, she became rapidly dyspneic and irrational, and evidence suggestive of atelectasis, pneumonia, or a combination was noted in the left lower lobe. Death occurred on the fourth day after operation. At necropsy † the entire left lower lobe was atelectatic, and there were areas of atelectasis in the left upper and right lower lobes. No pneumonia was observed either grossly or microscopically. The liver weighed 1835 gm. It was firm, yellowish brown and diffusely cirrhotic. The bone marrow in the shaft of the femur was red. Microscopic examination of the liver revealed a moderate degree of portal cirrhosis with marked periportal lymphocytic infiltration. The liver was quite fatty. The bone marrow exhibited normoblastic hyperplasia. Sections of the spleen revealed a remarkable prominence of the sinuses, quite similar to the "sinus hyperplasia" which was emphasized by Dürr<sup>26</sup> as a frequent finding in primary splenic fibrosis. Dürr regarded this as a fea-

\* These were referred to in part on page 1787.

† The writer is indebted to Dr. Ambrose Herzog of the Department of Pathology, University of Minnesota, for a report of the necropsy findings.

ture serving to separate Banti's disease from splenic enlargement secondary to cirrhosis of the liver. This could not be corroborated by the writer.<sup>27</sup> In the present instance it was impossible to decide whether the changes had been primary in the liver or spleen.

The eight cases mentioned above, in which evidence of blood destruction accompanied liver disease, were encountered in a group of 59 patients; 38 of these were believed to have cirrhosis of the liver, whereas 21 were classified as cases of "catarrhal" jaundice. Superficially, this suggests that the occurrence of increased blood destruction with liver disease is relatively rare. A considerable number of the patients, however, had marked "regurgitation" jaundice, with direct Van den Bergh reaction and bilirubinuria. In this group, of course, urobilinogen excretion in the feces is no longer of value in measuring the rate of blood destruction, except where the values are distinctly elevated in spite of a diminution in the outflow of bile.

The cases of Hodgkin's disease and leukemia associated with hemolytic anemia have been referred to elsewhere,<sup>30, 28</sup> so that this subject need not be considered further at this time.

#### SUMMARY AND CONCLUSIONS

1. Observations made in a series of 35 cases of hemolytic jaundice or anemia are discussed. Twenty of these cases were of microcytic type, 15 were macrocytic. Two of the latter group exhibited persistence of hemolytic anemia in spite of removal of associated pathologic conditions which might have been considered causal; in one of these cases splenectomy later resulted in cure.

2. Of most significance in distinguishing the familial or congenital from the secondary or acquired type is the predominance of microcytes in the former, and of macrocytes in the latter. This distinction should depend upon measurement of the average diameter of the erythrocytes, not upon simple inspection of the blood smears. Increased fragility was uniformly encountered in the congenital cases but was also observed in two of the patients with liver disease who had macrocytosis and increased blood destruction. Autohemagglutination was observed in two cases of macrocytic hemolytic anemia but in none of the cases of the familial variety.

3. In this series, jaundice and anemia were not found to increase in parallel fashion. Except for periods of hemolytic "crises" the opposite tendency was observed. In general it was true that the more jaundiced patients were the least anemic; in fact, the most jaundiced patient in the series was the least anemic, whereas the most anemic individual was not jaundiced. This suggests that a sluggish bilirubin excretory function of the liver, instead of being detrimental, may actually be of benefit in tending to prevent anemia.

4. The marked increase in circulating erythrocytes which is often observed immediately after splenectomy, is adequately explained by the pre-

operative effect of epinephrine on the spleen. Increases of the same magnitude may be produced with epinephrine in hemolytic jaundice before splenectomy. After operation the effect was not obtained.

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## CLINICAL STUDY OF THE ETIOLOGY OF OBESITY \*

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OBESITY is attributed to exogenous factors in most instances, but a few cases are thought to be of endogenous origin. Such appears to be the prevailing concept of the etiology of the malady. Newburgh,<sup>1</sup> on the other hand, contends that all cases of adiposity are caused by an energy intake which exceeds that of the body requirements. Factors favoring an excessive food intake have been studied by Harrington,<sup>2</sup> and Newburgh. They have noted the frequency of bad food habits and of desire for concentrated foods in obese patients. The activity of the patients during the gain in body weight, however, has been more or less neglected.

Endogenous adiposity has been attributed in most cases to alteration of the thyroid, pituitary or ovarian secretions, or to lesions in the hypothalamus.

The present study is concerned with, first, alterations in caloric intake or caloric requirement during the gain in body weight in obese patients; second, the incidence of evidence of ovarian dysfunction; third, the relationship of change in body weight to the onset of certain diseases of the hypothalamus and thyroid and pituitary glands; and fourth, the ability of obese patients to lose body weight when low caloric diets are followed. Cases of myxedema, pituitary tumor and chronic encephalitis were selected because corpulence in these diseases is usually cited to support the contention that alteration of the secretions of the thyroid and the pituitary glands or lesions in the hypothalamus are etiologic factors in obesity. Cases of two other diseases in which lesions of the hypothalamus may occur (suprasellar tumors and diabetes insipidus) were included.

### METHOD OF STUDY

The records of 350 cases of obesity, of which about one-third were personally observed, were studied for evidence of an increase of food intake or a decrease of activity during the time of gain in body weight. It is appreciated that histories of food intake are notoriously unreliable, but in a few instances the circumstances described by the patient justify the conclusion that there was an increase of food intake. A history of diminished activity is usually definite, particularly if it is caused by a long illness or convalescence. Ovarian dysfunction was considered to be present only if there was a history of abnormal menstruation.

The records of 100 cases of chronic encephalitis, 24 cases of myxedema, 22 cases of pituitary tumor, five cases of suprasellar tumor and seven cases

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of diabetes insipidus were analyzed for the incidence of obesity and for changes in body weight following the onset of the malady. Encephalitis had been present for at least one year in all instances, and the other diseases had existed for four months or longer.

The number of those obese patients who were known to have followed low caloric diets for a sufficient time and the percentage of those who lost weight satisfactorily were ascertained. The daily caloric value of the prescribed diets varied from 800 to 1500, but in all instances it was at least 1000 calories less than the patient's estimated 24 hour requirements. Such diets were followed for periods varying from one month to two years.

### RESULTS

Sufficient data were available regarding the food intake and activity during the gain in body weight in 154 cases. Gain in weight was associated with pregnancy or pregnancies without a history of increase in food intake or diminished activity in 32 instances. Most of these patients gained 15 to 25 pounds with each pregnancy, maintained the added weight, and thus became obese after three to six pregnancies. There were 13 patients who were either always obese or became obese without a history of change in activity or food intake. The gain in body weight which occurred simultaneously with diminished activity in 104 instances was accounted for in five cases by change in occupation, and in 99 others by a long illness, disability or convalescence. Accidents produced disability lasting from several months to two years in seven patients, a history of a long illness or convalescence following an operation was obtained in 17, a history of a long illness following pregnancy was present in 20, and 54 were ill or disabled for periods varying from months to years with psychoneurosis, heart disease, varicose veins, arthritis, hypertension, painful feet, diseases of the eyes which interfered with vision, residual paralysis after anterior poliomyelitis, etc.

Of 300 women, sufficient data regarding menstruation were available in 289. The menses were normal in 143 cases. Forty-eight had passed the menopause, but the obesity began several years prior to the change of life, and the menses had been normal during that time. In 191 cases ovarian dysfunction could apparently be excluded as an etiologic factor in the adiposity. Obesity began before puberty in five cases, but menstruation was normal. Adiposity began after the menopause in 15 instances, and antedated it in two. In these cases, however, the menses had been irregular for years. Menstruation was irregular in 34 patients and in four of these became irregular between the ages of 45 and 48 years after long standing adiposity. The menses were absent in 13, scanty in five, painful in seven and excessive in seven. The data are shown in table 1.

The incidence of obesity in myxedema, pituitary tumor, chronic encephalitis, suprasellar tumor and diabetes insipidus, and the relationship of

TABLE I

The incidence of, and types of, menstrual disorders, and the relation of onset of obesity to menopause and puberty are shown in the table. The number of these patients with various menstrual disorders who lost body weight when low caloric diets were followed is also shown.

Menstrual History and Relation of Menopause and Puberty to Onset of Obesity	Number	Number of Patients Who Lost Weight on Low Caloric Diets
Normal	126	60
Irregular	34	20
Nearing menopause	4	2
Dysmenorrhea	7	2
Menorrhagia	7	4
Scanty	5	4
Amenorrhea	13	6
Menopause	74	10
Obesity began after	15	6
Obesity began before	50	3
Menses were normal	48	3
Menses were abnormal	2	—
Artificial because of fibroids	4	1
Puberty		
Obesity began before	22	16
Menses normal	17	12
Menses abnormal	5	4
Obesity began with	1	1
Menses irregular	1	1

changes in body weight to the onset of these maladies are shown in table 2. It is to be noted that although the incidence of corpulence is high in these diseases, it was present in most cases before the onset of the other malady. It is also to be noted that patients with myxedema, pituitary tumor or chronic encephalitis became either more, or less, obese. Approximately as many patients lost weight as gained weight after the onset of myxedema and pi-

TABLE II

Shows the nutritional status of the patients at the time of examination, the relation of the obesity and the changes of body weight to the onset of the other maladies.

	Myxedema	Pituitary Tumor	Chronic Encephalitis	Suprasellar Tumor	Diabetes Insipidus
Nutritional status					
Obese	6	7	16	1	1
Thin	1	4	19	2	1
Normal	11	7	52	2	5
Relation of obesity to the onset of					
Antedated	4	5	16	1	1
Postdated	3	3	5	0	0
Disappeared with	1	1	5	0	0
Changes in weight after onset of					
Gained	6	5	6	1	0
Lost	5	7	33	2	1
No change	8	6	16	2	6

pituitary tumor, and loss of weight was five times more prevalent than gain in weight after the onset of chronic encephalitis. The patient with obesity and suprasellar tumor was obese for years before the cranial lesion produced any symptoms and continued to gain weight afterwards, whereas the patient who was obese prior to the onset of diabetes insipidus did not continue to gain weight.

Low caloric diets were known to have been followed for an adequate time by 146 patients, and all of them lost body weight satisfactorily. Several patients did not lose weight on low caloric diets at home, but in all instances they lost weight during and after hospitalization on the same diet. It is to be noted from tables 1 and 3 that the patients who lost weight on low caloric diets included those who had various menstrual disturbances, those who became obese from unknown causes and those who became corpulent with pregnancy, illness, operation, myxedema, pituitary tumor, chronic encephalitis and increased food intake. Adiposity developed in association with 36 different diseases or disabilities in the patients known to have lost weight satisfactorily. The patients listed under illness, table 3, became

TABLE III

Shows that obese patients who will follow low caloric diets for an adequate time will lose body weight regardless of the coexisting disease or the circumstances associated with the onset of the obesity.

Obesity Began in Association with	Number Who Lost Weight on Low Caloric Diets
Pregnancies . . . . .	22
Illness . . . . .	23
Impaired locomotion . . . . .	15
Operations . . . . .	10
Increase of food intake . . . . .	2
Chronic encephalitis . . . . .	3
Myxedema . . . . .	1
Hypophyseal tumor . . . . .	1
Insufficient data or negative history . . . . .	69

obese with heart disease, psychoneurosis, depressive psychosis and after long convalescences following pneumonia and typhoid fever. Those listed under impaired locomotion became obese in association with ununited fractures of legs, paralysis of legs following anterior poliomyelitis, painful feet, varicose veins, arthritis and impaired vision. The operations associated with gain in weight in these patients were cholecystectomy, appendectomy, thyroidectomy, removal of ovaries or ovarian cysts, hysterectomy and abdominal operations undertaken for reasons unknown. The patient with myxedema became obese after the onset of hypothyroidism. She remained in the hospital for one month on a low caloric diet without thyroid medication and lost 10 pounds in body weight. The patient with pituitary tumor and the two patients with chronic encephalitis also developed their obesity after the onset of these diseases, and all three lost weight satisfactorily.

## DISCUSSION

The high percentage of patients who gave a history of diminished activity while they were gaining weight indicates that many cases of "endogenous" obesity would be eliminated by a more detailed history. Illness or convalescence diminished the activity in most instances and corpulence very likely could have been prevented in these cases. It is just as important to prevent obesity as it is to relieve it, yet this phase of the subject has been emphasized comparatively little. The development of obesity with pregnancies in 20 per cent of these cases demonstrates the value of the practice of prevention of excess gain in body weight with pregnancy which has long been stressed. Corpulence could have been prevented in many of the 131 patients who became obese with pregnancies or with illness and convalescence. Adequate nutrition during a long illness or convalescence does not signify that the patient must become obese.

The theory that hypothyroidism is of etiologic importance in obesity has been discarded generally, but when adiposity develops in myxedema the lowered metabolism is usually considered to be an etiologic factor. The findings of this study indicate that the diminished metabolism is of little consequence in the etiology of the obesity. Patients with myxedema may gain or lose weight. A history of diminished activity with little or no impairment of appetite was obtained from two of the three patients who became obese after the onset of myxedema. Patients with coexisting myxedema and obesity will lose body weight satisfactorily when low caloric diets are followed for an adequate time.

The classic description of adiposity associated with hypophyseal tumor by Froelich<sup>3</sup> directed attention to the pituitary gland in certain cases of obesity. Many such cases have appeared since in the literature. The fact that as many of these patients lost as gained weight might be accounted for by a difference of pituitary secretions in hypophyseal tumors. The hormone liberated by the pituitary may be increased, normal or diminished in these cases. A history of diminished activity with a good appetite was obtained, on the other hand, from all those patients who became obese after development of hypophyseal tumor. One of these was known to have followed a low caloric diet and lost body weight. Such observations cast some doubt upon the etiologic importance of alteration of the pituitary secretions in the obesity of these patients.

The hypothalamus was incriminated in certain cases of adiposity when Smith<sup>4</sup> found that removal of the hypophysis in rats did not produce obesity unless the tuberal region was injured. Many case reports of obesity associated with chronic encephalitis have appeared in support of this contention. The development of obesity in five cases and its disappearance in five other patients after the onset of chronic encephalitis might be attributed to a different distribution and intensity of the brain lesions. A history of diminished activity with a good appetite was obtained, however, from three of

the patients who became obese after the encephalitis developed, and two cases in which encephalitis antedated the obesity were known to have followed low caloric diets and lost weight satisfactorily. Such findings indicate that encephalitic lesions of the hypothalamus played a minor rôle, if any, in the production of obesity in these cases. In addition, lesions of the hypothalamus apparently were not important factors in the production of adiposity in our cases of coexisting obesity and diabetes insipidus or suprasellar tumor. It is difficult to detect any difference between the obesity which develops in association with long inactivity due to a fractured leg and that which develops with a long illness due to pituitary tumor, suprasellar tumor, chronic encephalitis or myxedema. One has to admit, however, that not all patients with fractured leg, etc., become obese, but neither do all cases of myxedema, pituitary tumor and chronic encephalitis.

It is difficult to ascertain from the data available whether or not ovarian dysfunction was present in the patients with abnormal menses. The relationship of menstrual disturbances to obesity is also difficult to evaluate. Data are not available regarding the percentage of patients with menstrual disorders who become obese. Large numbers of these patients never gain excessive body weight. Amenorrhea, on the other hand, is not a common symptom and has been regarded as evidence of ovarian dysfunction. This symptom existed in six patients personally observed, and in all instances the menses returned after the loss of 10 to 100 pounds in body weight. The weight loss was accomplished by following low caloric diets without endocrine medications. Ovulation undoubtedly occurs in some of these cases of adiposity and amenorrhea. One such patient had not menstruated for seven years, yet she had three normal pregnancies at 1½ and two year intervals during that time. Another had amenorrhea for 2½ years prior to her last pregnancy. Ovarian dysfunction as an etiologic factor in the obesity of these cases is doubtful in view of the fact that patients with the different menstrual disorders lost body weight when low caloric diets were followed.

#### SUMMARY

The records of 350 cases of obesity have been analyzed for a history of increase of food intake or diminished activity during the time of gain in body weight, for evidence of ovarian dysfunction and for the ability of these patients to lose body weight on low caloric diets. In addition, the records of 100 cases of chronic encephalitis, 24 cases of myxedema, 22 cases of pituitary tumor, five cases of suprasellar tumor and seven cases of diabetes insipidus were analyzed for the incidence of obesity and for the changes in body weight following the onset of the malady.

Inactivity occurred simultaneously with gain in body weight in 67.5 per cent. A history of an increase in food intake, on the other hand, was obtained in only 3.2 per cent. A long illness or convalescence produced the

inactivity in 64.3 per cent. Ovarian dysfunction as evidenced by abnormal menses or menopause was present in 50.6 per cent.

The incidence of obesity in myxedema, pituitary tumor and chronic encephalitis was high, but adiposity antedated the other malady in most instances. The number of patients who lost body weight equaled approximately those who gained weight after the onset of myxedema and pituitary tumor. After chronic encephalitis developed, on the other hand, loss of weight occurred approximately five times as frequently as did gain in body weight. The etiologic rôle of alteration of the thyroid, pituitary and ovarian secretions, and of lesions in the hypothalamus is discussed.

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## MEDICO-LEGAL PROBLEMS OF HYPOGLYCEMIC REACTIONS IN DIABETES \*

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### INTRODUCTION

THE medico-legal aspects of insulin reactions in diabetics have not aroused the deserved interest in the medical world. Only two reports<sup>1, 2</sup> on this subject could be found in the literature. Despite the experience of physicians with the bizarre psychotic manifestations of hypoglycemia in their diabetic patients and the legal conflicts arising therefrom, it is surprising that the medical profession has neglected reporting such cases. Thus it is that 15 years after the introduction of insulin therapy there is still no standard legal precedent or procedure to handle such incidents.

There is, also, a profound sociological problem involved in each individual susceptible to hypoglycemic mental changes. His relation to the family, occupational group and society in general may have to be altered and adjusted adequately. His economic and social status may be disrupted by necessary restriction of his occupational activities to a limited field.

The increasing importance of this problem is apparent in the light of the continuously mounting incidence of diabetes and the increasing use of insulin among diabetic patients. This has been due to the wider acceptance of insulin therapy by patients and physicians and, in addition, to the advent of protamine insulin which has added many thousands to the ranks of those using insulin.

### OCCURRENCE OF HYPOGLYCEMIC REACTIONS

Every diabetic patient taking insulin, even though well controlled, may be subject to hypoglycemic reactions because of general intrinsic changes in tolerance as well as extrinsic, though transitory, factors such as sudden emotional expression, increased exercise, omission of meals, etc. Naturally, the poorly controlled diabetic with marked irregularity of the blood sugar level is more subject to reactions. It is obvious that the uncoöperative, "wild" diabetics, who exceed their dietary limitations or fail to adjust their insulin supply to the diet, will always present difficulties in management. In this group of poorly controlled patients, there must be included the "resistant" diabetic in whom the margin of safety between control and insulin overdosage is so narrow that hypoglycemic reactions are always imminent.

On the whole, the introduction of protamine insulin has reduced the incidence of hypoglycemic reactions. One is struck, at times, by the severity of the reaction with protamine insulin, apparently due to the prolonged release of insulin from the injection site. In addition, reactions with prota-

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mine insulin often lack those familiar premonitory symptoms such as palpitation, sweating, asthenia, etc., which warn of and prepare the patient for an impending shock. Further, the pressure of daily life with the possibility of disruption of the meal schedule may make the use of protamine insulin more hazardous in susceptible and very active patients because of its continuous action.

#### NEUROLOGICAL SYNDROME OF HYPOGLYCEMIA

The somatic symptoms of hypoglycemia, though important in precipitating legal complications, are overshadowed by the nervous and mental changes which contribute most to our topic. Interestingly enough, the somatic and central nervous system manifestations of hypoglycemia resemble strikingly the symptoms seen in high altitudes in mountain climbers, aviators, etc., where diminished atmospheric oxygen tension with resultant anoxemia is the acknowledged etiological factor. The analogy is now understood in the light of investigations<sup>3</sup> which have demonstrated a distinct decrease in oxygen utilization by the brain tissue during hypoglycemia. The neurological phenomena of hypoglycemia begin with vertigo, diplopia, tremor, and ataxia. Then follow paresthesias and hypalgesias, aphasia, twitchings, and rigor. Weakness or paralysis of any muscle group in one or more limbs, convulsions, epileptiform seizures, complete unconsciousness and deep coma are the final manifestations. One group, the "monosymptomatic," manifests the hypoglycemic reaction predominantly by one symptom, such as a tic, or diplopia, etc., whereas a variety or range of symptoms may be found in the "polysymptomatic." Furthermore, there are some who present a stereotyped repetition of symptoms with each episode, while others may display utterly different manifestations with each reaction.

#### MENTAL CHANGES

1. *Mild Cases.* There is a wide variety of mental changes displayed during hypoglycemia, from mild anxiety or exhilaration to severe psychotic states. The mild group of symptoms is initiated by irritability, anxiety, depression, exhilaration, or excitability. *Witzelsucht* and garrulity are rather infrequent. Partial disorientation and confusion, tendency to dawdle or loiter, and slowness of thought and action are commonly observed. Lack of will power and inability to make simple decisions may lead to typical *folie de doute* or *Entschlusslosigkeit*.

Any observer of diabetic patients could report countless examples of such mild mental manifestations. Therefore, only a few characteristic types will be cited for illustration. Relatives of some younger diabetics recognize the appearance of irritability, excitability, or hilarity as indicative of impending shock, and hence are experienced in taking prompt measures to abolish the reaction. Some diabetics appear morose, sullen and embittered, even asocial and misanthropic at the beginning of a hypoglycemic reaction. They

may refuse to sit with their families at the table or to engage in conversation and may even leave their company for the isolation of the bedroom. Here should be mentioned those children whose conduct may vary in the morning and afternoon classes in such a way, that ordinarily excellent and attentive pupils may exhibit inattention and misconduct during mild hypoglycemia. Exceedingly polite and considerate patients may display very rude and boorish behavior for short periods of time when hypoglycemic, and thus may jostle and push aside people on the street, without any evident reason, and in contrast to their normal demeanor, without even apologizing.

Some patients may have difficulties because of the slowness of thought and action accompanying hypoglycemia, and thus may arouse criticism from their foreman or employer. This is more significant in those patients whose work requires particular skill, such as weavers, seamstresses, typists, stenographers, etc.

The lack of will power and inability to make even the simplest decision is exemplified in those cases that, finding themselves on the threshold of hypoglycemia, are unable to take the food or sugar usually carried for such emergencies, even though this be in the pocket or in the hand. Many confusional and aphasic syndromes are reported by patients and their families, as typified by an incident wherein a boy misnamed the dishes at the dinner table, asking for ice-cream while indicating the butter, etc. Since this had happened before, the family recognized the cause and was able to abolish the reaction by feeding him sugar. Some children may use abusive language, or scold and berate their teachers, parents, or friends, such action presenting a transition to the more severe forms of hypoglycemic reaction.

Such mental changes may bewilder acquaintances and relatives who, familiar with the normal personality of the patient, are alienated by such strange and unusual actions. This abnormal behavior may give rise to serious social complications. The patient may be excluded from his circle of friends, business groups, or societies. The reaction may lead to very serious estrangements in the family with legal consequences. In one of our patients such bizarre behavior constituted sufficient grounds for a divorce action. Tillgren<sup>4</sup> reports a similar case in which hypoglycemic reactions caused the wife to ask for a divorce from her diabetic husband.

*2. Moderately Severe Cases.* The intermediate group of hypoglycemic mental changes presents exaggeration of the symptoms observed in the milder cases. Here are seen increasing difficulties of speech, thought, and action. Perseveration, confabulation, negativism, psychomotor hyperactivity, and pseudo-hysterical pictures up to hysterical opisthotonus are further manifestations. Maniacal behavior, acts of violence, exhibitionism, sexual perversity, compulsive laughter and crying, and impulsive actions follow increasing disorientation and confusion. Wanderings, delusions, hallucinations, melancholia, and paranoia, etc. are transitions to the severe group. As was pointed out in the neurological manifestations, here too, some patients may present one or two psychic pictures, and others a kaleidoscopic combina-

tion and variety of many of the above mentioned symptoms. This group is frequently characterized by partial or complete amnesia for actions committed during hypoglycemia.

In view of the limitation of space, only a few striking illustrations of this group will be presented. Many physicians have experienced difficulties in treating hypoglycemic reactions because of the negativism so common to this group. Not only may a patient refuse to take food himself, but he may even resist efforts by the physician, nurse or family to force food into him (R. M. Wilder<sup>13</sup>). It is not unusual for otherwise friendly and coöperative patients to strike physicians and nurses, when the latter attempt to administer treatment for the hypoglycemic reaction, and at times despite assistance, physicians have even been unable to administer glucose intravenously to such patients when violent agitation and partial confusion were manifest. In these cases it has been necessary to overpower the patients in order to permit the administration of glucose by the intravenous or oral route (stomach tube). A bizarre instance of negativism has been reported by Wauchope<sup>5</sup> in a man who insisted on driving his car home, with one eye shut (to obviate the diplopia), rather than eat the chocolate he carried with him.

Even more striking acts of violence and aggressiveness are common during hypoglycemia and may give rise to misdemeanor and assault. Thus, one of our patients, a very devoted mother, during hypoglycemia stuck a pin into her infant son's eye several times, mishandled and strangled him; only the intervention of her family prevented more serious injuries to the child. Kepler and Moersch<sup>14</sup> report the case of a severe diabetic who, while hypoglycemic, proceeded to shoot at his brother until he had emptied all the chambers of his gun. Fortunately he failed to inflict any injury. Another patient, an intelligent, well-mannered woman, has often been considered intoxicated when hypoglycemic in public because of her ataxia, confusion, abusive language, and belligerence.

Some patients, in a fury of devastation, break and shatter dishes, furniture, and household objects within their reach. One mother tearfully recounts the story of her diabetic son who in hypoglycemic frenzy smashes only expensive and prized possessions, such as a cherished vase or a valuable mirror. These cases reveal a certain amount of deliberateness or perhaps a kind of "pathologic logic" which directs the unconscious impulsive actions.

The release from inhibitions of moral, religious, or educational nature may allow full expression of repressed desires and pathological "drives." Exhibitionism during hypoglycemia is not uncommon. One of our younger diabetics undressed in public to the astonishment of bystanders. The earliest reports of insulin reactions by Oppenheimer,<sup>6</sup> Elias and Goldstein<sup>7</sup> related similar exhibitionistic tendencies. Other sexual aberrations have been observed. One severe diabetic, a young adult male, is greatly distressed by the hypoglycemic episodes which occur during or after coitus. Frequently the sexual act culminates with the patient in profound hypoglycemic shock, necessitating the immediate administration of sugar. More disturbing to

the patient and his wife, however, are the bizarre, sadistic, sexual perversions to which he is sometimes subject when hypoglycemia develops during intercourse. On recovery he is overcome with deep shame and embarrassment, inasmuch as his sexual habits are ordinarily normal. At times, because of partial or even complete amnesia, only the attitude and reaction of his wife, and the presence of bruises and scratch marks on her body, indicate to him that his behavior has been abnormal.

One of our patients, a 25 year old female, displays a variety of symptoms when hypoglycemic, acting as if intoxicated, becoming abusive and violent and on several occasions has outraged her family by defecating on the living room floor. Sexual abnormalities due to hypoglycemia have been reported here somewhat more fully in view of their obvious forensic importance. Except for exhibitionism, no attention has been paid to their significance heretofore.

The release from inhibitions during hypoglycemia may result in various actions foreign to the normal personality of the patient and may also be the basis of impulsive actions. An ordinarily moral and fanatically religious man has been known to blaspheme and abuse the church and God, astounding members of his congregation who could not understand the sudden change in his faith. A striking example of a compulsion during hypoglycemia was observed in one of our patients who was seized by an uncontrollable and irresistible urge to run through fast moving automobile traffic. With tremendous muscular effort he managed to cling to a lamppost, thus averting a serious accident. Such action might have accounted for the case of hypoglycemia reported by Sonne,<sup>8</sup> a diabetic who was struck by a trolley.

With further confusion and disorientation, the hypoglycemic patient may develop a *fugue* or "wandering state" which may last for a few hours. Even a keenly alert patient may not recognize the relationship of such mental clouding to the use of insulin, and may be ashamed to confess such an experience. One patient seized by a reaction while on his way to school wandered back home entirely disoriented, believing himself to be on the way to school all the time. Another case, while walking with his wife, apologized, left her abruptly and wandered about aimlessly for several hours, finally regaining mental clarity. On returning home he showed a complete amnesia for the events of the preceding hours.

It is evident that all these cases could have become involved in legal difficulties, were not their families or friends nearby to explain their actions on the basis of hypoglycemia. Such acts as destruction of property, assault, and sexual perversion are ordinarily subject to criminal law, and it is only because of the fact that patients commit them at home or among friends that they escape arrest. One of our patients, aware of the development of hypoglycemia, went to a candy store. There her violent agitation and loud demands for candy aroused the proprietor's suspicions that she was drunk. His refusal to sell her any candy made her so rabidly violent and abusive that her arrest was considered by the summoned policeman. Fortunately

her muscular activity resulted in an amelioration of the reaction, with restoration of her normal conduct, and with profuse apologies she was able to explain the hypoglycemic basis of her actions and avoided arrest.

3. *Severe Cases.* In this group of reactions we find intensification of the symptoms mentioned heretofore, up to completely psychotic states. Here, the complete disorientation and confusion, and the almost consistently complete amnesia, are characteristic features. The picture may resemble paranoia,<sup>9</sup> mania,<sup>6, 8, 9, 10</sup> catatonia, acute alcoholic delirium, Korsakoff's psychosis,<sup>11</sup> melancholia, etc. Naturally, the appearance of such severe syndromes is met with less often today because of the adequate training of the patients and their families, so that the usual therapeutic measures are taken before this stage is reached. These cases are so obvious that description is unnecessary. Some may be admitted to psychiatric institutions; one patient, a known diabetic with recurrent nocturnal maniacal episodes, so alarmed his family that in ignorance of the underlying hypoglycemia they called the police and had him transferred to a psychiatric hospital. Fortunately the transitory nature of such episodes precludes misinterpretation as to their etiology for more than a few hours, and the short course usually prevents very serious complications; nevertheless, during such episodes, even more than in milder confusion stages, actions may be committed which bring the diabetic face to face with the law.

#### FORENSIC SIGNIFICANCE

We have already referred to examples of hypoglycemic episodes in which legal complications arose. The first medico-legal case was reported by Fog and Schmidt<sup>1</sup> in 1931, nine years after the adoption of insulin therapy. Their patient, a truck driver, developed hypoglycemia while driving, and a serious accident occurred. By court order his driver's license was revoked because, in the opinion of the court, he did not possess the requirements of the Danish traffic law "as far as the mental abilities of an automobile driver are concerned." The next year, 1932, two cases were reported by Adlersberg.<sup>2</sup>

*Case 1.* K., 51 years of age, a very sedate business man, had been taking insulin for six years. After the usual injection of 30 units at 7:30 a.m. and breakfast, he went to his office one day and performed routine work. About 10 a.m. he took some fruit, and then made a few calls. At noon he went home for lunch by trolley. He had already had a "light dizzy feeling," and his companion told him the next day that he was amazed at the silliness and incoordinated movements of the patient at that time. The patient felt the need for sugar which, incidentally, he always carried with him but he lacked the "power and will" to take it. What happened thereafter he could not recall. The conductor and the police officer agreed as to the following: K. entered the trolley behaving like a drunkard, opened his vest, set his hat on the side of his head, yelled and laughed. The perplexed conductor called the police officer who ordered K. to leave the trolley with him. K. was obviously confused, resisted stubbornly, and had to be overpowered by the policeman who dragged him by force to the police station, followed by a curious crowd. He was rabidly violent.

Some time later, with decreasing disorientation and confusion, he begged the police to obtain some bread for him. This done, he was soon in complete possession of his senses, greatly surprised at his arrest and his preceding actions. The police surgeon examined him and found on him the marks of numerous injections, arousing vigorous protests on the part of the patient because of the accusation of morphinism. In court, his personal physician testified that he had been treating K. for some time and that similar confusions had occurred previously, but to a milder degree, and that probably this episode was due to hypoglycemia with transitory psychotic manifestations. The case was dismissed when evidence of previous similar episodes was produced.

Several times, while on the trolley, the patient had overlooked his point of destination, being slightly confused, was picked up at the end of the line, and brought to a police station where the officers already familiar with his behavior called his wife to take him home. A month before his arrest, while visiting relatives, he began to make stupid and silly remarks, a symptom very familiar to his family as indicative of a reaction. He fought off the attempts of his family to give him some food, and finally had to be overpowered by several people so that a few pieces of sugar could be forced between his teeth. A year prior to his arrest he had had a severe hypoglycemic reaction, after erroneously taking a double dose of insulin (confusing U 20 with U 40 insulin, a mistake not noted then by his wife). At dinner he behaved normally at first, but then towards the end he became completely psychotic. He danced about the table and juggled oranges. Soon after, he lapsed into coma from which he could not be aroused by the oral administration of sugar, but required hospitalization and intravenous glucose therapy. The reaction of the patient to these attacks was one of embarrassment and chagrin. He constantly proclaimed his innocence and insisted that the statements and stupidities uttered during hypoglycemia were beyond his control; that he could not even remember them. In fact, he was aware of them only through information gathered from his family. These accidents upset him greatly, for he was ordinarily very polite and correct, and could not understand how he could have been so rude and discourteous.

*Case 2.* T., a 37-year-old manicurist, had been taking insulin a half hour before meals for three years. When for any reason the meal was delayed she displayed anxiety, nervousness, and a striking pallor. She became discourteous and impolite without being aware of it, and allegedly, because of this change, lost several customers. During an examination, her physician once noticed signs of hypoglycemia (tachycardia, sweating, pallor, etc.) and was struck by her rude behavior. She became abusive, in contrast to her usual demeanor, cursed and swore. All these symptoms disappeared promptly after sugar was supplied. On learning of her conduct, she was visibly disturbed and admitted that similar episodes had happened before.

One day, after taking her mid-day dose of 30 units of insulin at the house of a customer, she proceeded home for lunch. On the way she began to feel slightly "dizzy" and therefore quickened her pace in order to reach home sooner. She crossed a busy street against the traffic light whereupon the policeman shouted something to her (she could not recall what). Then he approached and questioned her. She cursed the officer, refused to divulge her identity and resisted arrest. She was taken by force to the police station as a "drunkard." In a short time she regained full consciousness, was quite amazed to find herself arrested, explained everything and identified herself. She was arraigned in court and held in jail for 24 hours for "misconduct and insulting an officer."

In addition to these cases, we had an experience with a juvenile diabetic who was arrested for misconduct on the street during hypoglycemia.

*Case 3.* G., a 15 year old student, diabetic since the age of nine, had had mild

hypoglycemic reactions with regular insulin, at home and at school, which were easily controlled. When protamine insulin was instituted, the lengthy forenoon sessions of high school gave rise to difficulties in management. His breakfast was taken at 7:30 a.m. following the injection of 40 units of protamine insulin. School lasted from 8:30 a.m. to 2 p.m., an interval of six and a half hours of intensive activity without the usual noon meal. Despite warnings to take a light snack at 11 a.m., the boy was too lazy or embarrassed to leave the classroom, and often risked hypoglycemia by not eating until he reached home at 3 o'clock.

One day, this carelessness resulted in the development of hypoglycemia while on the way home, when he became ataxic and confused, shouted and sang. Passing individuals deplored the sight of such a young "drunk." At this point, a police officer took him to the station house, not without difficulty because of the violent resistance exhibited by the patient. At the station house the police emptied his pockets and found the yellow card of the New York Diabetes Association identifying him as a diabetic patient taking insulin and giving directions for the administration of sugar in such instances. Naturally, with the usual prompt recovery after sugar, he was discharged. Since then he has been more diligent in observing the proper spacing of meals, and no further conflicts have arisen.

Recently widespread publicity was aroused when the defendant in a case of a traffic accident in Brooklyn, New York, pleaded that insulin hypoglycemia with the consequent loss of central control had led to the accident. The court censured him for driving a car when liable to such episodes, and held that the State should refuse to license those taking insulin. For a few days thereafter the local press carried considerable discussion regarding the justification of such a measure. The divergence of opinion and the confusion evident in some of the editorials indicate the need for clarification of this problem by competent legislation. It is now obvious that even more serious crimes may be committed during hypoglycemia. Robbery, arson, and homicide must be admitted as possibilities for consideration in the field of medical jurisprudence. From the experiences of some of our cases, it is conceivable that even sexual crimes may be the result of psychic changes during hypoglycemia.

#### MEDICO-LEGAL CRITERIA

Establishment of the hypoglycemic origin of any criminal action must be based on the following facts:

1. Naturally, the evidence must show that the person took insulin, and especially at a time conducive to the development of hypoglycemia when the criminal act was committed. Thus with regular insulin we admit maximum action usually within 3 to 6 hours. Beyond 8 to 10 hours insulin reaction could hardly be invoked as an alibi. With protamine insulin the action is considerably prolonged and hypoglycemic accidents may occur even after 24 hours. Therefore, the increasing use of protamine insulin will complicate the medico-legal aspect of such incidents all the more, and proof of hypoglycemia will require chemical determination of the blood sugar level.

2. Evidence of hypoglycemia by clinical and chemical methods. The association of the well known somatic changes of hypoglycemia will tend to substantiate the diagnosis, and chemical corroboration will prove it. As to the latter, it is obvious that the tests should be done by a competent chemist, and an accepted standard method of analysis used.

3. The history of a contributory factor to the development of hypoglycemia is of importance, such as undue exertion or excitement, the omission of a meal or reduction of carbohydrate in the meal, or unusual delay in eating after the injection. However, we must admit that even without any such obvious reasons hypoglycemic reactions may develop in well controlled diabetics.

4. The history of any mental changes during previous hypoglycemic episodes, and particularly psychic manifestations resembling those leading to the legal difficulty in question.

5. The evidence that the actions during hypoglycemia stand in sharp contrast to the normal behavior of the involved person, as illustrated in all the above examples.

6. The presence of a partial or complete amnesia for the incidents in question. It is acknowledged that this is one of the most characteristic features of the hypoglycemic state, particularly when severe. The amnesia is most profound immediately following the reaction and later tends to clear up partially. This may be attributed in part to the tendency and ability of the patient to reconstruct the sequence of events from the conversation of witnesses. When confronted with the story of his actions, the hypoglycemic individual will display such a dramatic reaction of surprise and shame that this feature may distinguish real amnesia from a simulated one.

7. The prompt restoration of the normal personality with the administration of carbohydrate. This is, so to say, a therapeutic test.

As yet, no provocative test has been established which will precipitate a reaction for the purpose of observation by physicians or public officials. An obvious method would be the administration of an overdosage of insulin. In view of the rôle of cerebral anoxemia in the etiology of hypoglycemic reactions, perhaps as in aviation, tests under reduced oxygen tension may distinguish those diabetic individuals particularly susceptible to severe mental reactions.

When legal conflicts arise in such cases where hypoglycemia is proved, then the mental changes associated with this state are, we believe, sufficient grounds to consider the individual not responsible for his actions at such a time. This principle should be established and recognized by appropriate legislation. Of course, abuse of such laws by diabetic criminals will have to be considered, but careful medical analysis of each case should obviate such difficulties.

## LEGAL AND SOCIOLOGICAL ASPECTS

Having demonstrated the problems involving criminal law it is important to consider certain questions of civil law. It should be established that these patients are legally irresponsible during hypoglycemia. Thus, contracts and wills drawn up when the party is in a hypoglycemic state should be held invalid. Civil suits for libel and slander against diabetics should take into account the possibility of hypoglycemia. Divorce and breach of promise suits must be considered with this view in mind.

In addition, the question of licensure for different occupations involving public safety must be discussed. It is obvious that a diabetic, subject to severe hypoglycemic reactions, is unfit to drive a car, bus, locomotive, or airplane. A hypoglycemic reaction in one of these occupations may endanger not only the life of the diabetic driver but many innocent persons. Similarly, a reaction in a railroad switchman, traffic policeman, or lighthouse tender can cause untold damage to the unsuspecting public. According to various statisticians there are in this country more deaths from accidents than from all the contagious and infectious diseases combined, except tuberculosis. In view of the appalling death toll from this cause, an attempt must be made to weed out such individuals from all hazardous occupations. Stricter license tests would eliminate many drivers who are physically or mentally unfit. In this category must be included those diabetics who tend to develop frequent hypoglycemic reactions.

In the absence of adequate legislation, the physician as always must continue to be teacher and sociologist to his patients. He must urge a change or restriction of occupation when indicated, limitation of previous activities must be outlined, etc. We are familiar with the case of a surgeon who voluntarily restricted his professional activities to minor surgery, for fear of hypoglycemic reactions during major abdominal operations, which naturally required more time and exertion. Another physician gave up general practice for an administrative hospital position because the irregularities of his daily life were conducive to hypoglycemic reactions. The physician must caution those patients particularly susceptible to hypoglycemia against driving a car, working in critical occupations such as construction work, and indulging in strenuous sports, including mountain climbing and swimming. These patients should choose occupations of a sedentary nature, or at least indoor positions where they may be better protected against accidents and in which they are less apt to be a source of danger to innocent bystanders. This problem is of particular importance in the juvenile diabetics for whom vocational guidance must be intelligently applied, the children being trained in fields other than those which may expose them to undue hazard during hypoglycemic episodes.

## SUMMARY

In recent years hypoglycemic reactions have received wide medical attention. There are two groups with this syndrome:

1. Those with spontaneous hypoglycemia, either "idiopathic" or due to endocrine disturbances, and
2. Those diabetic individuals taking insulin.

It is interesting to note the accumulation of a voluminous literature on spontaneous hypoglycemia and its manifestations whereas the obviously more frequent hypoglycemia in diabetes has failed to arouse such interest. Although the absolute incidence of insulin reactions is greater than the literature would indicate, in the light of the innumerable insulin injections taken daily throughout the world it is relatively infrequent.

This report is concerned mainly with the mental changes of hypoglycemic diabetics because of the medico-legal importance of accidents arising from this state. From the mildest symptoms of anxiety and irritability to complete confusion and disorientation, the wide range of mental reactions has been presented and illustrated. An attempt at classification into mild, moderate, and severe cases has been made. The possibilities of legal conflicts arising from the somatic and mental changes of the hypoglycemic state have been emphasized and the need for appropriate legislative recognition of this problem has been stressed. The question of licensure for auto drivers, engineers, aviators, etc. has been discussed. Medico-legal criteria for actions committed during hypoglycemia have been established. The difficult and delicate sociological problems involved in each patient susceptible to mental changes during hypoglycemia have been outlined.

Until there is public recognition and appreciation of the legal and social aspects of these diabetic individuals the physician must continue his three-fold rôle of guide, teacher, and sociologist. He will have to educate the family, friends, and business associates of each patient as to the true nature of the personality changes during hypoglycemia. He must assist social agencies in adapting the patient to the necessarily altered circumstances of life.

The difficulties described should not stigmatize the diabetic patient as an inferior in our highly competitive society. It should be stated that the overwhelming majority of diabetics are capable of becoming an integral part of society, suffering no appreciable handicap, but on the contrary successfully fulfilling their obligations in all fields of human endeavor.

## CONCLUSIONS

1. Diabetic individuals, taking insulin, may present in hypoglycemia a wide variety of behavioristic and mental changes foreign to their normal personality.

2. Because of the somatic and mental changes manifest during hypoglycemia, actions may be committed which provoke conflicts with law and society.

3. Some uniform legislative procedure should be established to deal with such incidents.

4. The physician must continue to be guide, teacher, and sociologist to these patients who must adapt themselves to an altered life.

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## SPECIFIC SEROTHERAPY AND CHEMOTHERAPY OF THE PNEUMOCOCCUS PNEUMONIAS \*

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ADVANCES in the therapy of pneumonia have been occurring in recent years at an ever-accelerating pace. Nearly three decades elapsed from the earliest recognition of the etiological relationship of the pneumococcus to pneumonia in man and its first successful therapeutic application in specific serum treatment. This first step in the specific therapy of pneumonia was made possible through the subdivision of pneumococci into specific types. Therapy then became available for the most common of these types, namely, Type I. From the earliest use of specific antipneumococcus horse serums in the treatment of pneumococcus Type I pneumonia, it was recognized that, to be most effective, it was necessary to have potent type-specific serums, to give these serums intravenously in adequate amounts, and to use them early in the disease. Although constantly favorable results have been reported from individual clinics, this therapy did not receive widespread use because the treatment was cumbersome, the diagnostic procedures difficult and time-consuming, the available serums were of low potency, and the effect on the total fatality rate was so slight that it did not seem to justify the extensive use of the treatment.

*Concentrated Serums.* The introduction of methods for refining and concentrating the effective antibody contained in antipneumococcus horse serums and the gradual elimination from the concentrated antibodies of most of the substances responsible for the untoward reactions simplified the treatment and made possible an extension of the use of serum to include most patients with Type I and Type II pneumococcus pneumonias. The beneficial results of treatment in cases of Type I pneumonia became readily apparent with the use of these serums, but the results in cases of Type II pneumonia varied considerably, due in large measure to the low potency of the serums available for this type, even after concentration, and the inadequate dosage used.

*New Types of Pneumococci.* The classification of pneumococci formerly included in Group IV into the specific types IV to XXXII was the next great advance. With this new classification, strains formerly recognized by their atypical reaction with Types II and III serums were identified as the important specific Types V and VIII, respectively. When it became

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possible to identify the type of each pneumococcus regardless of its source, it was found that the new types varied considerably in the frequency with which they caused pneumonia or other infections, and also in the frequency with which they occurred as normal inhabitants of the respiratory tract in man. Most important, from the practical point of view, was the fact that a small number of these types was found to account for a considerable proportion of the cases of severe pneumonia, and for these common types, notably Types V, VII and VIII, therapeutic serums were prepared which were of high potency and were soon shown to be effective therapeutically.

With the aid of the new classification, it was also found that the types of pneumococci responsible for the majority of cases of pneumonia in infants and children were different from the types most frequent in the pneumonias of adults. Types XIV, VI and XIX were found to be the predominant types in the pneumonias of infants. It also became apparent that multiple types of pneumococci could be found in persons acutely ill with respiratory infections. Further experience permitted a practical interpretation of such findings which minimized the difficulties they presented. Certain types, notably Types I, II and V in adults and Types XIV, I and V in infants and children have been found quite consistently to bear an etiological relation to acute pulmonary infection. Other types, such as III, VII and VIII in adults and VI and XIX in infants, while etiologically related to many cases of acute pneumonia, have also been found frequently to be normal inhabitants of the nasopharynx without relation to acute disease. Still others, such as Types X, XX, and the types beyond XX, can usually be considered as part of the normal pharyngeal flora and only rarely give rise to acute pneumonia.

*Classification of Pneumonias.* With the extension of the use of specific serums to the newer types of pneumococci, it became more apparent than previously that the older classification of pneumonias into clinical anatomical entities, such as lobar pneumonia and bronchopneumonia, was no longer of any great significance. Many severe atypical pneumonias were found to be caused by common types of pneumococci. The etiological classification became the important one from the point of view of prognosis and therapy.

*Improvements in Typing.* Coincident with the developments and improvements in serum production and the extension of treatment to include the newer types, there were important advances made in the diagnostic procedures essential to the proper use of specific serums. The earlier methods of typing pneumococci usually involved waiting for the death of a mouse or sacrificing the animal injected with sputum after an interval of eight to 24 hours. The peritoneal exudate after that time frequently showed atypical or cross agglutinations. Errors were inevitable, valuable time was lost, and the efficacy of treatment reduced. The introduction of the Sabin microscopic method of agglutination from the peritoneal exudate of a mouse made possible more accurate type diagnosis within a period of three to six hours after a proper specimen of sputum was obtained. More recently the introduction of the Neufeld technic made possible type diagnosis directly from

sputum in about three-fourths of all cases within a matter of a few minutes of the time that a good specimen from a case of pneumococcal pneumonia arrives at a properly equipped laboratory. In specimens of sputum in which the pneumococci are rare, the application of this method to the peritoneal exudate, withdrawn three to five hours after a mouse is injected with the sputum, makes possible a type diagnosis in almost every instance. In cases in which sputum is not available, notably in infants and children, throat swabs incubated in proper media \* may be typed by this method directly after four to six hours, or the growth may be injected into a mouse in the same manner as sputum. This method of typing is also applicable to blood cultures. In such cultures, as soon as growth is recognized by the earliest color change, the type can be identified within a few minutes directly by this method.

*Rabbit Serums.* Within the past two years, antipneumococcus rabbit serums have been introduced into the therapy of pneumonia and have considerably broadened the scope of specific therapy and increased its efficacy. Experimentally many differences had been observed between antipneumococcus serums produced in horses and in rabbits. A number of them were considered to be of possible importance in therapy. While most of these advantages are theoretical, there are a number of practical considerations which make therapeutic rabbit serums an important contribution. (1) It is possible to produce effective serums more rapidly in rabbits than in horses, and these can be used with safety in the treatment of human cases. (2) For most types the titers of antibody are uniformly higher in rabbits than in horses. It thus becomes possible to give more effective doses in smaller volumes, and less time is lost. (3) It is more economical to produce serums for the less frequent types in the smaller animal. (4) The size of the antibody molecule has been found to be smaller in antipneumococcus rabbit serums than in horse serums of the same types (at least this has been shown for Types I and III). This offers the possibility of more effective penetration of the rabbit antibody into infected tissues and exudates. (5) It is possible to treat with rabbit serums patients who are specifically sensitive to horse serums, particularly those who have previously received horse serum injections, and many allergic reactions are thus avoided. Perhaps most important is the fact that for two of the most frequent types, namely, Types II and VIII, serums produced in horses have been of low potency, and in rabbits considerably higher concentrations of specific antibody for these types can be achieved. For Types I, V and VII, most horse serums have been fairly uniformly high in concentration and correspondingly efficacious.

In the use of Type XIV antipneumococcus horse serums an unusual number of reactions was observed, some of them serious and even fatal. It was found that serums of horses immunized with Type XIV pneumococcus have

\* Rabbit blood broth or serum broth may be used. Human ascitic fluid from nephrotic children has been found to be a favorable medium for this purpose at the Children's Hospital in Boston.

the property of agglutinating human erythrocytes of all blood groups. Antipneumococcus Type XIV rabbit serums were found not to have this property and are devoid of untoward reactions; thus they can be used safely. Nor were horse or rabbit serums for any of the other known types found to exhibit this unusual property.\*

*Standardization of Serums.* Advances have also been made in the standardization of serums. The earlier unconcentrated serums varied in potency as much as 100-fold or even more. The use of standard serums in the titration of the therapeutic products has introduced greater uniformity in the potency of the specific antibodies. The estimation of dosage with these standardized serums has been somewhat simplified.

*Sulfanilamide.* The widespread use of the newer chemotherapeutic agents, notably sulfanilamide, in various bacterial infections and the bacteriostatic effect of this drug on certain types of pneumococci in vitro have suggested the possibility that it might have some field of usefulness in the treatment of cases of pneumococcal pneumonia. Furthermore, the experimental evidence that sulfanilamide, in combination with specific serums, was more effective than either the drug or specific serum alone suggested the possibility that this combination might be a more effective method of treatment in certain cases of pneumococcal pneumonia where specific serums alone have not been found to be very effective. The high death rate from Type III pneumococcal infection and the relatively low potency of specific antibodies produced in both horses and rabbits for this type suggested the therapeutic application of the combined rabbit serum and sulfanilamide treatment in cases of pneumococcus Type III pneumonia. There appeared some evidence that sulfanilamide itself had beneficial effects on the course of such cases,<sup>1, 2</sup> and our own studies<sup>3</sup> indicated that its use in combination with serum is definitely superior to its use alone.

For other types of pneumococcus pneumonia, no clear evidence of the efficacy of this drug has been available until very recently when there has appeared a study indicating that it may have therapeutic value in some cases.<sup>4</sup>

*Sulfapyridine.* Recently sulfapyridine has been introduced into the therapy of pneumonia in Great Britain, and a number of reports have appeared in the British<sup>5</sup> and American literature<sup>6</sup> concerning the efficacy of this agent in the treatment of pneumococcal pneumonias. Striking results are reported in the treatment of infants and children, and reductions in death rate and beneficial clinical effects are also being reported in adults.

#### RESULTS OF SPECIFIC SERUM TREATMENT

At the Boston City Hospital we have tried to keep pace with these various developments. We have recently summarized the results of specific serum therapy in the treatment of pneumococcus pneumonia of Types I, II, III, V

\* FINLAND, M., and CURNEN, E. C.: Agglutinins for human erythrocytes in Type XIV antipneumococcal horse serums, *Science*, 1938, lxxxvii, 417-418.

and VII up to July 1938.<sup>7</sup> The early serums that we had available were experimental lots of low potency and produced reactions of varying severity in moderate numbers of cases. The more recent lots have been relatively free of untoward reactions and much higher in potency. This is particularly true of the recent therapeutic rabbit serums that we have had available for almost all types of pneumococci. The supply of the newer serums was also limited and their use was necessarily restricted to the severer cases or to early cases in order that some evidence of efficacy could be more readily acquired. As a greater supply of serums became available, a larger percentage of cases, particularly of the common types, were treated with serum, omitting only those cases that showed evidence of recovery or that had already died at the time the type was determined. In our compilations we have included all cases receiving the various therapeutic agents under consideration, regardless of the condition of the patient at the time of treatment and regardless of any complicating factors. We feel that this is of the utmost importance, since exclusion of some fatal cases is open to the interpretation that the therapy played some part in the outcome of the cases excluded. It is our feeling that such patients should be included and the deaths explained, since these cases form an integral part of the clinical disease which we are treating and since it is important to know under which conditions the various therapeutic agents are not effective or might possibly be harmful.

*Type I.* We may summarize briefly the results of specific serum therapy in the more common types of pneumococcus pneumonia up to the beginning of this season. In Type I pneumococcus pneumonia <sup>7a</sup> the percentage of cases included for treatment with serum increased during the last three years from 43 to 89 per cent. The mortality for all the serum treated cases has remained about 19 per cent, as compared to a 40 per cent mortality in the contemporaneous non-serum treated cases and in the non-serum treated cases for several previous years. The best results were obtained when treatment was started early so that in cases treated before the end of the fourth day the mortality for all cases was 13 per cent and for bacteremic cases 28 per cent. The severity of the entire group of cases is indicated by the fact that about 40 per cent of all of the cases chosen for treatment had blood stream invasion at the time treatment was begun. In this type, as in the others that we shall mention, all of the fatal treated cases are included in the calculation of the death rate. In most instances there were definite factors aside from the pneumonia contributing to the deaths. In a number of them the treatment was applied late and death occurred shortly after the beginning of therapy, and in others, death was due to complications either of the infection or not associated with the infection. It is possible, by exclusion of cases in which the treatment was obviously inadequate or where other factors contributed to mortality, to indicate a death rate in serum treated Type I cases as low as 3 per cent. This is more or less true for

most of the other types which we have had an opportunity to treat adequately with good specific serums.

*Type II.* In the Type II cases <sup>7b</sup> our results have varied during certain years and the poor results were attributed to inadequate therapy in terms of units of antibody per patient. During the past three years the percentage of Type II cases that we have included for specific serum therapy has increased from 33 to 82 per cent, and the mortality averaged 19 per cent among the 148 cases treated during this period. Among 121 consecutive cases treated before the end of the fourth day the mortality was 14 per cent in all cases and 27 per cent in the bacteremic cases. This compares with a 36 per cent death rate in contemporaneous non-serum treated Type II cases and, over a nine year period, a death rate of 40 per cent in all cases and 76 per cent in bacteremic cases. In this type also the severity of the cases as a group is indicated by the fact that 40 per cent of the cases included for serum treatment were bacteremic cases. Since it has been repeatedly shown that the institution of serum therapy prevents the occurrence of bacteremia in patients in whom such invasion has not yet occurred at the time treatment is begun, this percentage of bacteremic cases is more significant than if it were found in non-serum treated cases. In a small series of cases treated with rabbit serums during the last year of this study, the results were even more striking than those previously demonstrated with horse serums.

*Types V and VII.* In the cases of Types V and VII pneumococcus pneumonia <sup>7d</sup> the reduction in death rate has been greater than in either of the two commoner types, I and II. This has been especially true for Type V pneumococcus pneumonias which at the Boston City Hospital have been associated regularly with a high mortality (40 per cent) and a high bacteremic incidence before specific serums for this type became available. This figure for mortality is somewhat higher than that reported from other clinics, which is usually given as about 25 per cent. In the 81 cases of Type V pneumococcus pneumonia treated with specific serum before July 1, 1938 (almost all of these were treated with horse serums), there were only eight deaths, or 10 per cent; and 33 per cent of the cases were bacteremic. The non-serum treated case fatality rate for the previous nine year period was 41 per cent with a 43 per cent bacteremic incidence. Prior to July 1, 1938, there were 79 cases of Type VII pneumococcus pneumonia treated with serum with nine deaths, a mortality rate of 12 per cent. This compared with an average contemporaneous and previous mortality rate of 29 per cent in 160 cases not treated with serum. Twenty per cent of the Type VII treated cases were bacteremic as compared with 24 per cent of the non-serum treated cases of this type. When treatment was begun before the end of the *fifth* day of illness, the death rate was 7 per cent among the Type V cases and 3 per cent in the Type VII cases.

*Type VIII.* The results in our cases of pneumococcus Type VIII pneumonia have not yet been reported in detail. During the first season that serums for this type became available, they were produced in horses, were

of low potency, and frequently gave reactions of moderate severity. Of 11 cases treated with such serums there were four deaths. Although only the sickest patients were chosen for treatment and the dose of antibody used was grossly inadequate, these results can be considered definitely poor. During the following year rabbit serums were available for most of the cases and were of higher potency than the horse serums, and both the rabbit and horse serums were considerably freer of reactions. During that year 30 cases were treated with three deaths, the latter occurring in hopeless cases. The average death rate for cases of pneumonia due to this type during the past 10 years has been about 25 per cent.

These figures, although indicating a definite and marked reduction in death rate as a result of specific serum therapy, do not reflect the entire picture. In the first place, the clinical response to this treatment has been striking. In pneumonia of these five types treated with serum, in about 80 per cent of the cases a clinical crisis has been induced within eight to 36 hours of the beginning of treatment. We have already called attention to the fact that there have been important factors contributing to the failures in the Type I cases, leaving only a small residual where the specific treatment could be said to be ineffective. The same was true for the other types.

*Type III.* We have recently reviewed the results of treatment in cases of Type III pneumococcus pneumonia treated with sulfanilamide or specific serum or with a combination of these two agents.<sup>7c</sup> The results, as reflected in the death rate, were not very striking, but there was definite evidence from an analysis of the clinical results in these cases and from bacteriological and immunological studies<sup>3</sup> that the pneumococcal infection was definitely benefited.

*Higher Types.* Serums for a number of the higher types became available during the last two years. As in the more common types, the supply available at first was limited and only the most severely ill patients were chosen for treatment. During the present season, however, we have had available a supply of horse and rabbit serums of high potency for a number of types and have treated a small group of patients with results that have been similar to those previously observed with the more common types, as we shall note later.

*Sulfanilamide.* We have not made any systematic study of the use of sulfanilamide except in the cases of Type III pneumonias already mentioned. We have used this drug in conjunction with specific serum in some of the severer or complicated cases of pneumonias due to the commoner types, and alone in a number of cases due to the higher types when specific serums were not available. In the pneumonias due to the common types<sup>7</sup> sulfanilamide was continued in those cases in which treatment with the drug was begun before typing was obtained, when the patients were seemingly benefited. In most instances, however, specific serums were given to cases of these types because the clinical condition of the patient had not shown adequate improvement with the drug. The number of cases treated with

sulfanilamide alone are too few to warrant any conclusions. In general, the clinical results were not striking. Nor was there any sharp reduction in death rate noted over previous years. Among 43 cases treated, there were 16 deaths (37 per cent). Six of the deaths were among the 11 bacteremic patients. It is interesting to note that three of the bacteremic cases that recovered after sulfanilamide therapy had Type XII pneumococcal pneumonia. In most of the patients who recovered following treatment with sulfanilamide, the termination of the acute illness did not seem to be in relation to the therapy.

#### RECENT RESULTS OF TREATMENT WITH SULFAPYRIDINE AND SERUM USED ALONE OR IN COMBINATION

Probably the greatest interest at the moment concerns the results obtained during the present season with the use of sulfapyridine alone or in combination with specific serums. Since early this fall we have used this drug in the treatment of 175 adult patients with pneumonia due to specific types of pneumococci. Eighty of these patients received specific serums in addition. Since July 1, 1938, we have also treated 167 cases with specific serums alone. The three groups of patients are not entirely comparable. It was natural, having available specific agents of known efficacy, that only milder cases were first chosen for treatment with the drug alone. This is reflected in the relatively low bacteremic rates as compared with the groups of patients treated with serum alone. Likewise, inasmuch as experimental evidence pointed towards a greater efficacy of the drug when used in combination with specific serums, it was natural that this treatment was chosen for the more severe cases, namely, the bacteremic patients, particularly those in the older age groups.

*Mortality in Relation to Age and Bacteremia.* The distribution of cases according to type of treatment received, the age, and the results of blood culture are shown in table 1. In the 167 cases treated with serum alone there was the usual incidence of bacteremia, averaging 27 per cent,\* and, as usual, bacteremia was more frequent in the older age groups. The death rate in this group of cases was 13 per cent. Among the cases treated with sulfapyridine alone, the bacteremic incidence was only 17 per cent, and in the older patients the relatively infrequent occurrence of bacteremia indicates that we were dealing with a definitely milder group of patients over 60 years of age. For the entire group of 95 patients, the death rate was 15 per cent. This probably indicates a definite reduction in fatality rate over that which might be expected in patients not treated with specific serums or chemicals. Considering the relative bacteremic incidence, however, these results may be considered as probably inferior to those obtained with serum alone.

\* All bacteremic rates refer to the results of blood cultures before the institution of therapy.

TABLE I

Cases of Pneumococcic Pneumonia Treated at the Boston City Hospital  
July 1, 1938 to March 15, 1939

Age Group	Bacteremic		Non-Bacteremic		All Cases			Per Cent Bacteremic
	Number	Died	Number	Died	Number	Died	Per Cent Died	
Cases Treated with Serum Alone:								
12-19	8	1	24	0	32	1	3	25
20-39	15	2	56	2	71	4	6	21
40-59	17	9	36	3	53	12	23	32
60+	5	3	6	1	11	4	36	45
All	45	15	122	6	167	21	13	27
	33% Died		5% Died					
Case Treated with Sulfapyridine Alone:								
12-19	—	—	14	1	14	1	7	0
20-39	4	0	23	2	27	2	7	15
40-59	9	3	24	1	33	4	12	27
60+	3	3	18	4	21	7	33	14
All	16	6	79	8	95	14	15	17
	38% Died		10% Died					
Cases Treated with Specific Serum and Sulfapyridine:								
12-19	1	1	—	—	1	1	—	—
20-39	6	1	8	0	14	1	7	43
40-59	17	9	21	4	38	13	34	45
60+	16	5	11	1	27	6	22	59
All	40	16	40	5	80	21	26	50
	40% Died		13% Died					

The group of 80 patients chosen for treatment with the combination of sulfapyridine and serum contained a greater proportion of older patients and the incidence of bacteremia was about twice that in the patients treated with serum alone and three times that in the cases treated with sulfapyridine alone. It is to be expected that the fatality rate in such a group of patients would be considerably greater than in the first two groups. The total bacteremic incidence in this group was 50 per cent. Eighty-one per cent of these patients were over the age of 40, and 34 per cent were over 60 years of age. Among the 27 patients over 60, 16 or 59 per cent were bacteremic.

Nevertheless, in this latter group the mortality rate was only 22 per cent. In similar cases treated without specific serums or drugs we have found, over a number of years, that the expected fatality rate in this age group with this bacteremic incidence is between 75 and 90 per cent. With specific serums alone, it is 50 to 60 per cent.<sup>7, 8</sup>

*Results in Different Types.* The number of cases of each type are too few to consider in detail. The results for each of the common types and for all the higher types are shown in table 2. Two interesting features may be pointed out. Of 14 Type I cases over 60 years old and treated with serum and sulfapyridine, 12 were bacteremic and only 4 died. Among the cases

TABLE II  
Pneumococcic Pneumonias Arranged by Type

Type	Serum Alone*				Sulfapyridine Alone				Serum and Sulfapyridine			
	All Cases		Bacteremic Cases		All Cases		Bacteremic Cases		All Cases		Bacteremic Cases	
	Num-ber	Died	Num-ber	Died	Num-ber	Died	Num-ber	Died	Num-ber	Died	Num-ber	Died
I	50 <sup>6</sup>	4 <sup>1</sup>	13 <sup>1</sup>	3 <sup>1</sup>	33	3	9	2	33	8	19	6
II	24 <sup>1</sup>	6 <sup>1</sup>	8 <sup>1</sup>	3 <sup>1</sup>	2	0	0		17	4	10	4
III	9 <sup>6</sup>	2 <sup>1</sup>	2 <sup>1</sup>	2 <sup>1</sup>	26	4	4	2	16	3	2	2
V	18 <sup>4</sup>	3 <sup>1</sup>	4	2	6	1	1	1	4	1	3	1
VII	20 <sup>2</sup>	3 <sup>1</sup>	4 <sup>1</sup>	2 <sup>1</sup>	6	0	0	—	3	0	1	0
VIII	18	1	6	1	6	0	1	0	3	2	1	0
Other Specific Types	28 <sup>3</sup>	2	8	2	16	6	1	1	4	3	4	3
All Types	167 <sup>20</sup>	21 <sup>5</sup>	45 <sup>4</sup>	15 <sup>4</sup>	95	14	16	6	80	21	40	16
Per Cent Died	13		33		15		38		26		40	

\* Includes patients who received sulfanilamide in addition. The numbers are shown by superscripts

due to types other than I, II, III, V, VII and VIII there were five deaths in the 32 cases that received serum, including the four cases treated with sulfapyridine in addition. These 32 cases included 13 with bacteremia and 16 over 40 years of age. It is worth mentioning here that all five of these fatal cases had important factors other than the pneumococcic pneumonia which contributed to the fatal outcome. It may also be noted that the only two bacteremic cases of Type III pneumonia who recovered were treated with sulfapyridine alone. We have previously noted three recoveries in bacteremic cases of this type treated with sulfanilamide alone.<sup>70</sup>

The present results are, therefore, most encouraging. It is obvious that it will be necessary to have a considerably larger number of cases in each

category before final conclusions can be reached as to the relative efficacy of the drug and serum alone or in combination. From the practical point of view, it is evident that *both specific serums and sulfapyridine are effective agents*, and that in severe cases the use of the combination of the drug and specific serum has shown definite effects in reducing the fatality in the severest group of patients in which the mortality is the highest.

*Clinical Response.* From the point of view of the clinical response, our experience has led us to expect that when good type-specific serums are given in adequate amounts a rapid deffervescence of the symptoms of acute disease takes place within six to 24 hours in the great majority of the patients, and they look and feel completely relieved of symptoms. With the use of sulfapyridine alone, the patients manifest evidence of illness for a considerably longer period, and this is particularly true in the patients with the severer illness associated with bacteremia. Furthermore, the possible antipyretic as well as the toxic effects of this drug make the proper evaluation of the course of the disease difficult. We have found that the use of the drug alone, in all but the mildest cases, must be continued for a minimum of 48 to 72 hours or even longer after the deffervescence of fever. In patients treated with a combination of serum and sulfapyridine, if adequate doses of both are used, the drug can be dispensed with in periods varying from 12 to 36 hours after the initial dose, and probably much smaller doses of serum are necessary than when the drug is not used. It has, therefore, been a great comfort to see severely ill patients whose prognosis is extremely poor manifest evidence of complete recovery within a few hours after the beginning of therapy with drug and serum.

It is not possible at this time to present a detailed account of the dosage used in various cases, the results of the estimations of the blood concentrations, and the toxic effects observed. In general, we have used doses similar to those employed by others. We have noted variations in absorption and in the toxic effects. In a number of mild cases, rapid recovery has occurred when it was obvious that practically no absorption of the drug took place, as evidenced by the low or even undetectable concentrations attained in the blood. Such cases make the evaluation of the data difficult until a large number of cases are available for analysis of all the factors entering into mortality as well as the evaluation of the clinical course under different types of therapy.

*Untoward Effects.* As to toxic effects, we have noted most of the untoward symptoms already noted by others. Nausea was most prominent and occurred in about two-thirds of the cases. In about one-half of those with nausea there was vomiting, which varied in severity, and in about one-half of the latter this symptom was severe enough to interfere with further oral administration of the drug. Intravenous injections of saline and glucose were found to be of only slight help in some, but not all such cases. Moderate anemia has occurred early in a number of cases but the progressive type of anemia noted with sulfanilamide has not been noted

frequently, presumably because the drug has usually been discontinued after a shorter period. Cyanosis was less frequent and less marked than with sulfanilamide. One fatal case of agranulocytosis was observed in a 19 year old boy not included in the above tables since no pneumococcus type was obtained in his sputum, the causative agent being a staphylococcus. In this patient there was total absence of granulocytes in the blood 36 hours after onset of therapy and death occurred 12 hours later. Severe mental and physical depression and, in some cases, marked excitement have been noted during the administration of this drug, even when the infection has apparently improved. Impaired renal function is one of the important complications which we have noted, although the evidence to implicate the drug is not complete. In one case there was nitrogen retention and edema, and in a second, nitrogen retention and mental and motor manifestations of uremia. In these two cases the evidence of renal impairment occurred after the patient had been on treatment for more than four days and after the acute infection had obviously subsided, and when the pulmonary lesion showed evidence of clearing or had completely cleared. Both these patients died. Neither had received serum.

A number of cases have already been encountered in which, after treatment with sulfapyridine alone, relapse of the pneumonia occurred in the same or other portions of the lung. The same or other types of pneumococci or other organisms, notably hemolytic streptococci, were recovered during the relapse. Such relapses have occurred three to 10 or more days after complete subsidence of fever and after what was considered to be an adequate dose of the drug.

Our experience is as yet too limited to permit a detailed discussion of both the beneficial results and the failures of treatment with sulfapyridine. The failures of specific treatment and its limitations have been adequately discussed on many occasions, and the circumstances under which this treatment alone is most effective have been detailed. The introduction of rabbit serums has widened the scope of effectiveness of these specific serums. Similar studies in adequate numbers of cases treated with sulfapyridine alone and with a combination of sulfapyridine and serum will need to be carried out and analyzed in great detail before the complete scope of usefulness and the limitations of the drug alone or in combination with serum and the relative efficiency of these various types of treatment can be evaluated. Furthermore, the results must be assessed for each of the specific pneumococcus types.

In the meantime, we feel that in the therapy of the pneumococcus pneumonias, we now have two very effective agents—specific serum and sulfapyridine. The abandonment of specific serum in favor of the drug alone would be unfortunate at this time. For the present, and until more data become available, we feel that the following procedures represent the method of choice for the treatment of patients with acute pneumonia:

(1) Each case should have adequate bacteriological control, including sputum examination with smear, culture, and typing, and a blood culture should be made *before any serum or drug is administered*. It is to be borne in mind that negative blood cultures taken after treatment with either serum or drugs like sulfanilamide or sulfapyridine give a false sense of security and are not of the same prognostic significance as positive blood cultures obtained before such treatment is instituted. After any serum therapy there is frequently a transient sterilization of the blood stream for six to 24 hours. If an adequate dose of specific antibody has been given, the blood remains free of bacteria unless focal complications already exist. After sulfanilamide or sulfapyridine has been given, the bacteriostatic effect of the drug may serve to prevent the growth of small or moderate numbers of bacteria which may be present in the blood.

(2) Complete blood counts should be made, urine analysis should be done, and blood non-protein nitrogen determined before treatment and frequently thereafter when sulfapyridine is used.

(3) Treatment with sulfapyridine may be started in all cases as soon as the diagnosis of pneumonia is established. It is recommended that patients with polynuclear neutropenia should not be treated with this drug until more information becomes available to indicate that treatment of such patients with this drug is safe. Leukopenia with a high percentage of polynuclear leukocytes is probably not a contra-indication to the use of the drug. Likewise, until it is definitely shown that patients with jaundice or with known or suspected liver or renal disease can tolerate this drug, it is probably wise to avoid treating such cases with sulfapyridine.

(4) In adult patients over 40 years of age and in all pregnant or recently parturient women in whom any of the common types of pneumococci are found, and in all cases in which the blood culture yields specific types of pneumococci, specific serums should be given as soon as possible to insure the most effective therapeutic response unless, at the time when the results of the blood culture or typing are available, there is already definite evidence that the acute disease has subsided. Treatment with adequate amounts of serum helps to insure complete and rapid recovery without recrudescence.

In the choice of specific serums for therapy, it may be said that uniformly beneficial results are obtained only when highly potent serums free of any but the milder reactions are used in adequate amounts, and that when serums of low potency are given in relatively small doses and result in frequent and severe reactions the beneficial effects of the serums are greatly reduced. It is our feeling that the wide variations in results obtained with specific serums can be explained in large measure on this basis.

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## RECENT ADVANCES IN THE TREATMENT OF PELLAGRA AND ASSOCIATED DEFICIENCIES \*

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IN 1735 Gaspar Casal, a Spanish physician, first described pellagra and shrewdly pointed out that this disease is related to an inadequate diet.<sup>1</sup> That diet was the controlling factor in the etiology of the disease was not suggested again until the work of Goldberger, Waring and Willets<sup>2</sup> in 1915. During the next two decades, the full significance of diet in the development of pellagra gradually became evident because of the frequent association of the disease with faulty nutrition. Later, the administration of a high caloric diet, rich in protein and vitamins, supplemented with large amounts of antipellagric materials such as yeast, wheat germ or liver extract, became the accepted form of therapy.<sup>3, 4, 5</sup> Although beneficial in most cases, this treatment is often impractical. It frequently necessitates hospitalization of the severely ill patients for several weeks, during which time almost constant supervision by a physician, nurse or dietitian is required. Furthermore, many of the patients who improve following this therapy are unable to buy, after discharge from the hospital, the relatively expensive foods which will protect them against recurrences of the disease. In addition, failure to recognize pellagra in its subclinical or mild form continued to be an obstacle to effective and lasting treatment, as advanced pellagra often developed before a diagnosis was made and therapy instituted. It is not surprising, therefore, that efforts have been directed toward obtaining a more practical form of treatment, toward developing methods by which an earlier diagnosis can be made, and toward identifying and isolating the anti-pellagric factors.

A little more than a year ago, Elvehjem, Madden, Strong and Woolley<sup>6</sup> reported that nicotinic acid and nicotinic acid amide are effective in curing blacktongue in dogs, a canine disease considered by many investigators to be an analogue of human pellagra. These observations suggested the possible therapeutic value of these compounds in pellagra and stimulated many investigators to study their effectiveness in treating this disease. As a result of the dramatic improvement of several symptoms of the disease reported by all workers in the field,<sup>7-10</sup> nicotinic acid became an accepted part of pellagra therapy. Its discovery has made possible great advances not

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only in the treatment of pellagra but also in the study of some of the fundamental chemical processes involved in its development.

For ease of description, the recent advances in our knowledge of pellagra will be divided arbitrarily into those concerned with: Therapy in the classic case; the vasodilator effect of nicotinic acid and related anti-pellagric compounds; the recognition and therapy of subclinical deficiencies in adults and in children; and the evidences of multiple deficiencies in pellagrins subsisting on their usual deficient diets.

#### THE THERAPY IN THE CLASSIC CASE

During the past year and a half, nicotinic acid has been used in treating hundreds of cases of classic pellagra. In this type of case, the outstanding symptoms arise from the skin, the alimentary tract and the nervous system, although all three systems are not necessarily involved nor do the symptoms appear in any regular order.<sup>20</sup>

Characteristic glossitis usually appears early in the course of the disease. In the early stages the tip and lateral margins of the tongue are reddened and swollen. As the involvement of the mucous membranes increases, the swelling and reddening become more intense. Deeply penetrating ulcers are common, and their surfaces are often covered with a thick, gray membrane filled with Vincent's organisms and debris. Stomatitis, gingivitis and pharyngitis likewise may develop and follow a similar course. Burning sensations of the mouth, esophagus and stomach may accompany these oral lesions, and are aggravated by hot or acid foods. Nausea, vomiting, ptyalism and diarrhea, which are frequently present in the severely ill pellagrin, often appear in the sub-clinical case. Anorexia, abdominal distention, pain and discomfort are common symptoms and may be present at any stage of the disease. Dr. Leon Schiff and Dr. Richard Stevens, of the University of Cincinnati School of Medicine, have performed gastroscopic examinations on two pellagrins and noted that the diseased mucous membranes of the stomach are similar in appearance to those of the oral cavity. The mucous membranes of the urethra and vagina are frequently swollen and ulcerated, and appear identical to the affected portions of the alimentary tract.

The dermal lesions of pellagra may develop on any part of the skin although the dorsa of the hands and feet, the axillae, elbows, wrists, knees, areas beneath the breasts, and the perineal region are the most common sites. The lesions are usually bilaterally symmetrical and are separated from the healthy skin by a sharp line of demarcation. At the onset, the affected area is erythematous and often burns and itches severely. Later it becomes swollen, tense, and often fiery red. Sometimes vesicles and bullae develop. After a variable period of time, ranging from a few days to several months, the swelling decreases, the color becomes reddish brown, and desquamation begins. The underlying skin may remain abnormally thickened and permanently pigmented.

Various types of psychoses occur. The most common symptoms are confusion, loss of memory, disorientation and confabulation. One frequently sees excitement, mania, depression and delirium.

The presence of certain symptoms arising from involvement of the peripheral nervous system which, in themselves, are not diagnostic of pellagra frequently helps to confirm the diagnosis. The pellagrin often complains of burning, numbness and tingling of the extremities long before any diagnostic symptoms of the disease appear. (These symptoms are characteristic of peripheral polyneuritis; indeed, pellagrins often have co-existing beriberi.) As the disease in the peripheral nerves increases, alteration of the tendon reflexes occurs; at first their activity is increased, later decreased, and finally absent.

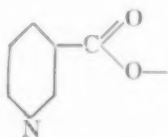
The administration of adequate amounts of nicotinic acid or one of its compounds is followed by the disappearance of many symptoms of the disease. Within 24 to 72 hours, the fiery redness and swelling of the tongue, gums, mouth, throat, and vagina subside, and the associated Vincent's infection disappears. Within 24 to 72 hours, nausea and vomiting cease, increased salivation decreases, and bowel movements become normal. Abdominal distention, pain and discomfort disappear and, in most cases, the desire for food returns. The acute, fiery red erythematous dermal lesions in which the epithelium is intact blanch within 48 hours after the administration of nicotinic acid, but where the continuity of the skin is broken and the lesions are moist, ulcerated, dry or pigmented, there seems to be no specific benefit. Perhaps the most dramatic response of a pellagrin to nicotinic acid therapy is the disappearance of the acute mental symptoms.<sup>13, 15, 17, 18, 21, 22, 23, 24</sup> These symptoms, varying from slight confusion to delirium and mania, disappear rapidly, often over night. The maniacal patients become calm and the confused patients, mentally clear. After therapy they become readjusted, and often have excellent insight and memory of their actions, ideas, and surroundings during the psychotic period. Apathy and lassitude give way to interest. In sharp contrast to the prompt and beneficial response of the mental symptoms to nicotinic acid is the lack of improvement in symptoms arising from the peripheral nervous system. The administration of crystalline vitamin B<sub>1</sub>, however, gives prompt relief from these symptoms.

Nicotinic acid, nicotinic acid amide, and sodium nicotinate are all effective in the treatment of pellagra. They may be administered orally in tablet or capsular form, or parenterally in physiological solution of sodium chloride. Unless the powers of absorption are greatly impaired, oral administration is preferred. Opinion in regard to dosage differs. Although the dosage probably varies considerably in different pellagrins, experience with a large series of cases has shown that 500 milligrams daily, administered orally in 50 milligram doses, is a safe and effective dose for the average case of pellagra. We have observed that only 50 milligrams daily may be required by the mild case but that in rare instances as much as 1000 milligrams per day may be re-

quired for the very severe case. Administered parenterally, the total daily dose varies from 40 to 80 milligrams, dissolved in sterile physiological solution of sodium chloride and injected intravenously, in divided doses of 10 to 15 c.c. each. The dosage of nicotinic acid amide and sodium nicotinate is similar to that of nicotinic acid.

#### VASODILATOR EFFECT OF NICOTINIC ACID AND RELATED ANTI-PELLAGRIC COMPOUNDS

It has been noted by a number of investigators<sup>11, 14, 15, 17, 18, 19, 24, 25</sup> that the administration of large amounts of nicotinic acid to human beings is often followed by sensations of heat and tingling of the skin. This feeling of heat is accompanied by flushing and a rise in skin temperature, especially over the face. Bean and Spies<sup>26</sup> have worked out a method whereby comparable objective determinations may be made. They have found that in normal adults increased temperature of the skin follows the intravenous injection of 20 milligrams of sodium nicotinate, ammonium nicotinate, ethyl nicotinate, and the monoethanolamine salt of nicotinic acid, as well as nicotinic acid itself. This response does not occur following the use of pyridine, quinolinic acid, dinicotinic acid, 2,6-dimethyl dinicotinic acid, beta-amino pyridine, or beta-amino pyridine dihydrochloride. The administration of substances which provoke the vascular response is frequently followed by some epigastric distress, increased peristalsis, and occasionally belching. Observations<sup>26</sup> also show that glycine, under certain circumstances, tends to inhibit this vasodilator reaction. The subcutaneous injection of 1 c.c. adrenalin tends to prevent the elevation of skin temperature following the administration of these drugs. From a study of the structural formulae of these compounds, it is probable that the vascular reaction is associated with the following radical:



Thus, it is evident that the chemicals effective in pellagra therapy do not invariably produce the flushing, although those provoking the temperature rise are all effective therapeutic agents.

#### THE RECOGNITION AND THERAPY OF SUBCLINICAL DEFICIENCIES IN ADULTS AND CHILDREN

The development of severe pellagra can, in most instances, be avoided if the disease is recognized in its early forms and treated appropriately. It is apparent, from a study of many pellagrins, that there is a long prodromal period of ill health. This period has insidiously advancing symptoms, all trivial in nature, but gaining in importance by their persistence. Loss of

weight, strength, and appetite precede the appearance of any diagnostic oral or dermal lesions. During this early stage, ill-defined disturbances of the alimentary tract, including indigestion, "dyspepsia," diarrhea or constipation, as well as weakness and lassitude develop without obvious reason. Irritability, depression, loss of memory, headache and insomnia are noted. Other early symptoms characteristic of a deficiency of the anti-pellagric factors include abdominal pain, burning sensations in various parts of the body, vertigo, numbness, nervousness, palpitation, distractibility, flight of ideas, apprehension, and mental confusion. There is obviously much that is abnormal but nothing which is pathognomonic. The entire syndrome of vague, grumbling complaints appears to be without objective cause and if a patient is seen at this stage of the disease and pellagra is not suspected or suggested, a diagnosis of neurasthenia may be entertained by the physician.

An early diagnosis of pellagra is made possible by the recognition of these prodromal symptoms if they are associated with prolonged subsistence on an inadequate diet; if they occur in persons who have difficulty in ingesting, assimilating, or utilizing food because of organic disease; or if they appear in persons whose requirement for anti-pellagric substances is increased by pregnancy, lactation, hyperthyroidism, infection, or increased physical exercise. The development of clinical pellagra can be prevented in these subclinical cases by the administration of adequate amounts of nicotinic acid. Following its administration these persons experience an increase in sense of well-being and vigor almost immediately. Indigestion is relieved, nausea ceases, and bowel function is restored to normal. Nervousness, irritability, and mental confusion disappear rapidly following adequate dosage, and the vague burning sensations in various parts of the body disappear soon after treatment is initiated. Although improvement in symptoms arising from the alimentary tract and cerebral cortex is striking, many of the pellagrins develop polyneuritis which becomes worse in spite of continued therapy with nicotinic acid or related compounds. (The administration of massive doses of nicotinic acid does not relieve either the painful symptoms of beriberi, arising from involvement of the peripheral nerves, or the symptoms of riboflavin deficiency which arise from the lesions around the mouth, nose, eyes, and ears, whereas the administration of synthetic thiamin hydrochloride and synthetic riboflavin, respectively, is followed by prompt disappearance of these symptoms.)

The amount of nicotinic acid needed to relieve these early symptoms and to prevent the development of clinical pellagra cannot be predicted, nor can it be determined other than by frequent examination of the patient. The amount needed by an individual may vary from time to time and often it is necessary to adjust the dosage to meet this changing need. There is also considerable variation in the amount needed by different patients. As little as 50 milligrams daily may be effective in some cases, while 500 to 1000 milligrams is sometimes required in others, although this is seldom necessary. The therapeutic effect of these substances is proportional not only

to the total dosage, but also to the size and frequency of the individual dose. That is to say, the oral administration of ten doses of 50 milligrams each at hourly intervals is more effective than a single dose of 500 milligrams. This suggests that the controlling factor is the concentration of compounds of nicotinic acid in the blood and tissues.

Observations on the children in several hundred "pellagra families" have shown that many of these children have early clinical signs of pellagra.<sup>15, 24</sup> Such children often have a history as follows: For years they have been somewhat below normal in weight and height; their progress in school has been slow; their inability to concentrate is apparent; and they have few interests. Frequently they complain of poor appetite, indigestion, vomiting, soreness of the tongue and lips, and constipation. Their parents report that they are cross, "fretful," and cry easily. A careful check on the dietary history of the family often shows that the diet of the mother during pregnancy was inadequate and that shortly after birth the child had to be given food of some sort as the mother gave insufficient milk; hence, from a short time after birth, such children have frequently been a "feeding problem." In addition, many of these children show a preference for only one or two foods and refuse all others. The diet is usually rich in carbohydrates, and when milk, eggs and meat are included, they rarely are given in sufficient amounts. When the children have clinical evidence of the disease as shown by characteristic glossitis or dermatitis, there can be no question of the diagnosis, and nicotinic acid therapy is as effective as it is in adult pellagrins. However, spectacular improvement following therapy with nicotinic acid or some closely related anti-pellagic compound has been noted in many children who have subsisted over long periods of time on an inadequate diet but who show none of the diagnostic symptoms of pellagra. In general, the complaints of these children have been similar to those of adults. Likewise, the method of study was similar but the amount of nicotinic acid given was less. Within 24 to 36 hours after the administration of nicotinic acid there was prompt improvement in general health and disappearance of the various complaints. Usually, these children were given a total daily dose, varying from 50 to 300 milligrams. We recommend that this total dose be given in from 5 to 10 tablets at least one hour apart. Children from two to six years of age are usually given tablets of the 10 milligram size, and those up to puberty are given tablets of the 25 milligram size. In treating clinical beriberi and clinical riboflavin deficiency occurring in these children, we gave one-half the amount of synthetic thiamin hydrochloride and synthetic riboflavin recommended below for an adult.

*Abnormal Metabolites.* The appearance of various abnormal metabolites can be detected by laboratory methods before, during, and after the development of the prodromal symptoms of pellagra. Determination of the presence of these metabolites is an important objective test for the recognition of pellagra.

The excretion of abnormal amounts of indican in the urine of pellagrins

is indicative of a disturbance in tryptophane metabolism.<sup>27</sup> Disturbance of porphyrin metabolism is an important part of the pellagra syndrome, as evidenced by the excretion in the urine of pellagrins of increased quantities of porphyrin, and porphyrin-like substances which are ether-soluble red pigments and can be extracted in 25 per cent hydrochloric acid.<sup>28, 29, 30</sup> The content of nicotinic acid derivatives excreted in the urine of pellagrins is greatly decreased during the prodromal period.<sup>31</sup> Similarly, the concentration of cozymase, an enzyme which is fundamental to cellular respiration, is below normal in the blood and urine of severe pellagrins in relapse.<sup>32, 33</sup> The content of vitamin B<sub>1</sub> is often lowered in the urine of pellagrins with beriberi, and the amount of flavin in the urine likewise is decreased in pellagrins with riboflavin deficiency.

#### EVIDENCE FOR MULTIPLE DEFICIENCIES IN PELLAGRINS SUBSISTING ON THEIR USUAL DEFICIENT DIETS

In contrast to the extensive literature on the mental changes of pellagra, relatively few observations have been reported on involvement of the peripheral nerves. While studying so-called "alcoholic" pellagra, Spies and DeWolf<sup>34</sup> came to the conclusion that alcohol is not the sole cause of the peripheral neuritis affecting such pellagrins. The correctness of this point of view has been established by a number of observers. It has also been established that the peripheral neuritis of endemic pellagrins is beriberi and is due to lack of vitamin B<sub>1</sub>.<sup>17, 18, 19, 24, 35</sup>

Still more recent studies on a large series of pellagrins subsisting on their usual inadequate diets, have shown that the administration of nicotinic acid in adequate amounts prevents or improves the alimentary tract symptoms, the erythematous dermal lesions, and the mental symptoms of pellagra, but that it does not prevent, retard or relieve the symptoms of peripheral nerve involvement. These symptoms, however, are relieved when adequate amounts of crystalline vitamin B<sub>1</sub> are administered. Crystalline vitamin B<sub>1</sub> may be administered either orally or parenterally, depending upon the patient's ability to absorb it. For the mild case of pellagra with peripheral neuritis we recommend the oral administration of 10 milligrams twice a day. Severe cases should receive at least twice this amount. The parenteral administration of 50 milligrams daily, in physiologic solution of sodium chloride, by intravenous injection, is preferable in the very severe case as it shortens convalescence and affords prompt relief from pain. The administration of vitamin B<sub>1</sub> should be continued until after improvement has taken place. The acute case will often show improvement within a few hours and the mild case, within 24 to 48 hours. Chronic cases often experience relief from pain within a few days, but some of the abnormal physical signs may remain for a long period of time.

Studies on 25 white and 5 colored ambulatory patients in the nutrition clinic at the Hillman Hospital during 1938-39 show that riboflavin deficiency

occurs in either sex at any age and is not uncommon in persons ingesting, over a considerable period of time, a grossly inadequate diet. It has been pointed out by Sebrell and Butler<sup>36</sup> and by Vilter, Vilter and Spies<sup>32</sup> that this deficiency state is characterized by a feeling of ill health, lack of strength, and loss of weight. Diagnosis depends upon the recognition of characteristic angular stomatitis associated with transverse fissures in the corners of the mouth and lips, and an abnormal shiny redness of the mucous membranes of the lips. Other diagnostic lesions, occurring less frequently, are the comedones giving a "sharkskin" appearance from collections of greasy, seborrheic material around the *alae nasae*, eyes, and occasionally over the ears and malar prominences. Some of these patients give a history of visual disturbances. These symptoms disappear within four to six days following the administration of riboflavin\* in adequate amounts. The minimal and optimal therapeutic dosages have not been determined, but we have found that the oral administration of from 5 to 50 milligrams per day is effective and it seems likely that even smaller doses may be beneficial. Riboflavin is a safe therapeutic agent when administered either orally or intravenously (in sterile physiological solution of sodium chloride). Improvement in these lesions is associated with an increased sense of well being. If these patients continue to eat only their usual diet, the symptoms usually return within 10 to 20 days after the administration of riboflavin is discontinued. (The diet which as a rule consists of corn bread, biscuits, corn syrup, and fat meat, is deficient in riboflavin.) Four patients who were not treated improved temporarily while eating their usual diet at home, but in other untreated cases the lesions slowly and steadily became worse as spring advanced. The daily addition of synthetic riboflavin to the diet of 10 patients has prevented the reappearance of these lesions during the past three months. Two patients have been treated with the phosphoric acid ester of riboflavin,† injected intravenously, with spectacular improvement. Riboflavin deficiency may occur in association with beriberi or pellagra, or it may appear without clinical evidence of either.

The content of coenzyme I and II in the blood and urine is altered little, if any, by the administration of any of the riboflavin preparations tested so far.

The time has come when we are forced to accept the belief that clinical pellagra, clinical beriberi, and clinical flavin deficiency are responses of the body to deprivation of these essential chemical substances over a long period of time. Within our own group we have used the terms "chemical pellagra," "chemical beriberi," and "chemical flavin deficiency" to describe that stage between optimum nutrition and the frank appearance of diagnostic evidence of the particular disease; that is, the period which might be termed the deficiency development time. The latter portion of this period has been

\*Furnished through the courtesy of Dr. Hans Molitor and Dr. Randolph Major of Merck and Company, Rahway, New Jersey.

† Supplied through the courtesy of Dr. O. W. Barlow and Dr. J. B. Rice of the Winthrop Chemical Company, Rensselaer, New York and New York City, New York.

called the prodromal period and is characterized by many vague symptoms of subclinical deficiency states. In such early stages a diagnosis of neurasthenia is apt to be made, yet these symptoms disappear following the administration of specific therapeutic agents.

#### DIETARY STUDIES

From an analysis of the dietaries of 50 pellagrins<sup>37</sup> we have learned that in almost every instance, as is shown in the following table, the pellagrin has ingested a diet which is inadequate in calories, protein, calcium, iron, vitamins A, B<sub>1</sub>, G, and, to a lesser extent, vitamin C. The deficiency of calories is manifested in the underweight of the average pellagrin, and the lack of protein, particularly protein of high biological value, is sufficiently pronounced to lead to the edema observed in some cases. The extent of vitamin B<sub>1</sub> and flavin deficiency in the food consumed by these persons is in direct support of our observations that although these dietaries are supplemented with sufficient amounts of nicotinic acid, forestalling the development of alimentary disturbances and mental symptoms of pellagra, the polyneuritis of beriberi frequently develops; and that if adequate supplements of both nicotinic acid and vitamin B<sub>1</sub> are added, preventing the development of pellagra and beriberi, clinical evidence of flavin deficiency develops in some persons. The inadequacy of vitamin A, calcium, phosphorus and iron is

A Comparison of the Nutritive Values of the Dietaries of Pellagrins with Standards for Normal People

Nutrient	Calo-ries	Pro-te-in	Minerals			Vitamins			
			Ca (gm.)	P (gm.)	Fe (mg.)	A (I.U.)	B (I.U.)	C (I.U.)	G (Sherman-Bourquin units)
Standard* { 19 men	3000	67	.68	1.32	15	5600	150-385	150-375	600-800
27 women	2500	75	.88	1.20	13-15	5600	125-300	125-300	500-800
3 children									
boy—13-15 yrs.	3000	75	.88	1.32	15	5600	150-385	150-375	600-800
boy—4-6 yrs.	1500	55	1.00	1.00	8-11	4200	75-188	100-250	300-650
child under 4 yrs.	1200	45	1.00	1.00	6-9	4200	60-150	100-250	240-600
Per cent patients below standard	97	95	83	85	98	93	95	42	94
Range in per cent below standard	17-91	5-86	7-92	5-92	7-90	1-100	20-100	4-100	17-100
Average per cent below standard	35	50	61	58	51	67	72	47	73

\* From "Quantities of Nutrients for Individuals per Day to Be Used in Evaluating the Adequacy of a Diet"—Dr. Hazel Stiebeling, Bureau of Home Economics, U. S. Dept. Agriculture.

probably accountable, in part, for the general ill health of the patients, although the symptoms of specific mineral or vitamin A deficiency are obscured by the more dramatic symptoms of other deficiencies, or it may be a question of better storage and assimilation of these nutrients. Nicotinic acid, vitamin B<sub>1</sub> and flavin apparently are not stored in the body in available form for a long period of time, since daily supplements given in two or more doses are more effective than the same amount given in one dose or the same amount given at longer than daily intervals.

Preliminary studies concerning the precise physiological effect of synthetic nicotinic acid, riboflavin and its phosphoric acid ester, and cocarboxylase (the pyrophosphate of thiamin) have been undertaken and are summarized below:

Methods, devised independently by Kohn<sup>33</sup> and Vilter, Vilter and Spies,<sup>18, 32</sup> measure the cozymase, a diphosphopyridine nucleotide, and coferment, a triphosphopyridine nucleotide, in blood to approximately one part in 200,000,000.\* Application of this method to pellagrins in relapse shows that their blood and urine contain only a small fraction of the normal concentration of these codehydrogenases. Within 24 to 48 hours after giving large doses of nicotinic acid, there is a striking increase in the concentration of these codehydrogenases in the blood and urine. At the same time that the cozymase and coferment are increasing, improvement occurs clinically. These observations support the hypothesis that nicotinic acid is effective as an anti-pellagic agent, at least in part, through its effect on these codehydrogenases.

Using the extraction method of Emmerie<sup>38</sup> we have noted that the fluorescence of the flavin compound normally excreted in the urine differs somewhat from that produced by equal concentrations of synthetic riboflavin or the phosphoric acid ester of riboflavin, dissolved in water, or in the acid-water-pyridine mixture used in the extraction of urine. Riboflavin and its phosphoric acid ester have a yellowish-green fluorescence, while the flavin compound normally excreted in the urine has a bluish-green fluorescence which is different from the above. When equal molecular quantities of riboflavin or riboflavin phosphoric acid ester are given intravenously, the amount of flavin excreted in the urine during the next few hours is markedly increased and its yellow-green fluorescence is identical with the fluorescence of the synthetic substances. The following day the amount and fluorescence of the flavin extracted from the urine of patients given unphosphorylated riboflavin are essentially the same as they were before therapy. However, the urine of patients given the phosphoric acid ester of riboflavin contains at this time, and for several days thereafter, more extractable flavin than was found during the control period, and this flavin also has the blue-green fluorescence of the flavin compound which is excreted normally. (The quantities are measured with a photoelectrometer and not with a fluorometer because the amount of fluorescence is not directly related to the concentration.) These results might be interpreted as showing that synthetic riboflavin and the synthetic phosphoric acid ester of riboflavin act differently in human beings.

Synthetic cocarboxylase † has been administered intravenously to four

\* We are very grateful to Professor H. von Euler, Biochemiska Institutet, Stockholm, Sweden, for a sample of pure cozymase; and to Herr Geheimrat Doctor Otto Warburg, Kaiser Wilhelm Institut für Zellphysiologie, Berlin-Dahlem, Germany, for pure coferment and pure cozymase.

† Furnished by Dr. Hans Molitor and Dr. Randolph Major of Merck and Company, Rahway, New Jersey.

selected cases of nutritional polyneuritis. The deficient diets of all the patients remained constant throughout the period of study. The administration of synthetic nicotinic acid to two of the patients who had alimentary tract symptoms and skin lesions characteristic of pellagra, was followed by prompt improvement of these pellagrous symptoms but not of the peripheral neuritis. By the end of two weeks the peripheral neuritis had become much worse, and the patients were given sterile physiological solution of sodium chloride for two days without relief from pain. The following day two 10 milligram doses of cocarboxylase were given within two hours, and eight hours after the second dose the patients were relieved of pain. The two patients with clinical beriberi but without co-existing clinical pellagra likewise received no benefit following the injection of sodium chloride, but were relieved promptly after they were given cocarboxylase. These studies show that the intravenous administration of cocarboxylase is effective in relieving pain from nutritional polyneuritis. They do not imply, however, that this material is more effective per unit of weight than is crystalline vitamin B<sub>1</sub>. Cocarboxylase might have some special therapeutic indication, provided the body was unable to phosphorylate vitamin B<sub>1</sub> as a result of liver impairment or some other disease.

Synthetic nicotinic acid, synthetic thiamin hydrochloride, and synthetic riboflavin, as specific therapeutic agents, are invaluable in treating the acutely ill patient for they may be given when it is impossible for the patient to take sufficient vitamin-rich food to make up for these deficiencies. It appears that the improvement in patients with pellagra following the administration of nicotinic acid, in patients with beriberi following the administration of thiamin hydrochloride, and in patients with flavin deficiency following the administration of riboflavin, is brought about by the changing of synthetic substances to enzymes. These, in turn, act through the usual biochemical oxidative-reductive systems in the body. They do not, however, replace all the essential nutrients, and a liberal, well-balanced diet should be given as soon as the patient can take it. These relatively cheap synthetic substances are also valuable as supplements to a diet which, because of economic reasons or poor dietary habits, is inadequate, and in cases where the requirement is increased to such an extent that it cannot be met by food alone.

#### SUMMARY AND CONCLUSIONS

The accumulated information of the past two decades indicates that pellagra is a clinical syndrome caused primarily by a nutritional deficiency, and that certain predisposing and precipitating factors play a rôle in the pathogenesis of the disease. Prominent among these are fatigue, insomnia, loss of teeth, infectious diseases, food fads, chronic alcoholism and diseases affecting the alimentary tract. Failure to recognize the above mentioned conditions in proper light has often led to the designation of such cases as "pseudo pellagra," "secondary pellagra," and "alcoholic pellagra." From

the standpoint of therapy such terms are confusing and should be abandoned, for the disease either is or is not pellagra.

In the absence of the diagnostic triad of cutaneous, alimentary and nervous manifestations, diagnosis of pellagra may be difficult. However, an atypical case may not involve this combination of symptoms but can be recognized when any one of these major systems is affected independently of the other two, and if the possibility of other forms of dermatitis, other diseases of the digestive system, and other diseases of the nervous system is excluded.

An early diagnosis of pellagra is dependent upon a reliable interpretation of an accurate history and a careful physical examination. In the presence of any of the vague symptoms characteristic of the prodromal period subclinical pellagra should be suspected, particularly if there is a history of an inadequate diet. The disease in its subclinical forms is common in both adults and children in poverty-stricken areas where persons live on unbalanced diets low in protein, minerals and vitamins. Early diagnosis and treatment will prevent the development of clinical pellagra.

The appearance of various abnormal metabolites in the urine of pellagrins in relapse and of subclinical pellagrins is an indication of the development of the disease. Detection by laboratory methods of these abnormal metabolites excreted in the urine of pellagrins before, during and after the development of pellagra forms an important objective test for early recognition of the disease and is an aid toward understanding some of the fundamental chemical processes involved.

Preliminary studies directed toward eliciting the precise physiological effect of synthetic nicotinic acid, riboflavin and its phosphoric acid ester, and cocarboxylase have been summarized.

Nicotinic acid or one of its closely related compounds, when administered in adequate amounts, has a prompt and beneficial effect on certain symptoms of clinical and subclinical pellagra. In cases of acute or chronic pellagra in relapse it will: (a) cause fading of the fiery red lesions of the mucous membranes and diminish the Vincent's infection associated with it, (b) in most cases, restore to normal disturbed gastrointestinal function, (c) restore to normal the mental function deranged moderately or severely in acute pellagra, (d) cause fading of the dermal erythema but not cure chronic changes of the skin. In cases of subclinical pellagra, the vague ill-defined symptoms disappear and in persons subject to recurrences of the disease the development of clinical pellagra is prevented. In both clinical and subclinical pellagra, the sense of well-being, one of the attributes of health, is restored. The necessary therapeutic and prophylactic dose varies considerably from patient to patient and from time to time, and is increased by infection, forced physical exercise, and fever. It can be determined only by frequent examination of the patient. The administration of these substances may produce certain typical reactions which, although they may be unpleasant, are transitory and have not been associated with any grave com-

plications nor have they been shown to be harmful in amounts needed for effective anti-pellagric therapy.

Nicotinic acid has no apparent effect upon the peripheral neuritis which is so frequently associated with pellagra. Pellagrins restricted to a pellagra-producing diet and nicotinic acid frequently develop peripheral neuritis, whereas pellagrins with peripheral neuritis who are maintained on a similar diet supplemented with vitamin B<sub>1</sub> but not with nicotinic acid show improvement in their peripheral neuritis, but not in their mucous membrane lesions, alimentary symptoms, erythematous dermal lesions or mental symptoms. However, neither nicotinic acid nor vitamin B<sub>1</sub> will prevent pellagrins from developing evidence of riboflavin deficiency. In view of this it would seem that pellagrins tend to have not only a deficiency of nicotinic acid or substances that act similarly, but also a deficiency of at least two other water-soluble vitamins, vitamin B<sub>1</sub> (thiamin hydrochloride) and riboflavin. The clinical evidences of these deficiencies are a result of the deprivation of these substances over a long period of time. "Chemical pellagra," "chemical beriberi," and "chemical flavin deficiency" are terms suggested to describe the deficiency development time. Whether additional active substances are involved can be determined only by further investigation.

Nicotinic acid, thiamin, and riboflavin are invaluable in treating the pellagrin who has a deficiency of thiamin and flavin. Detailed studies of the food consumed by pellagrins reveal inadequacies of most of the essential nutrients. It is imperative, therefore, to stress this fact that these chemical substances, although invaluable as therapeutic agents, cannot be expected to replace a liberal and well-balanced diet.

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## ATROPHY AND NECROSIS OF THE LIVER WITHOUT JAUNDICE \*

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JAUNDICE is probably the symptom which leads all others in attracting attention to hepatic disease. In its absence, the occurrence of ascites, pruritus, hematemesis, melanoderma, or enlargement of the liver or spleen may indicate the presence of hepatic disease. There are, however, many hepatic conditions not associated with these symptoms and signs and, in such cases, diagnosis must rest largely on suspicion. In the recognition of subclinical cases, a clue is frequently obtained from careful scrutiny of the history and close observation of the patient. In doubtful cases, a review of possible etiologic factors may lead to further search for proof of the presence of a disorder of the liver. The development of various tests for liver function has aided materially in the early recognition or confirmation of the suspicion of hepatic disease.

The cases to be discussed are characterized by the absence of jaundice, are subacute or chronic in nature and illustrate the value of tests for liver function in diagnosis. These cases cannot be correlated definitely with the usual classification of diseases of the liver. Short illustrative reports of cases are presented under the following arbitrary headings: (1) atrophy of the liver associated with disease of the gall-bladder and biliary tract; (2) atrophy associated with syphilis or with its treatment; (3) atrophy of exogenous toxic origin, and (4) atrophy unassociated with other diseases.

### ATROPHY ASSOCIATED WITH DISEASE OF THE GALL-BLADDER AND BILIARY TRACT

*Case 1.* A man, aged 62 years, was first seen at The Mayo Clinic in July 1934. He had had typhoid fever in 1891 and, for 20 years, he had experienced flatulent indigestion. Biliary colic had occurred on two occasions. On physical examination his condition was found to be satisfactory. Cholecystographic examination revealed a poorly functioning gall-bladder containing many stones. Operation was advised but was deferred. The following year he was seen again. Because of vague general symptoms and some decline in health, a bromsulphalein test of liver function was done; results indicated a retention, grade 3 (on the basis of 1 to 4). The van den Bergh reaction was indirect. The concentration of bilirubin was 1.9 mg. per 100 c.c. of serum. Operation again was advised and again was deferred.

This patient related a history of long-standing cholecystic disease and there was evidence of liver dysfunction without jaundice. The latter possibly could be attributable to: (1) a silent stone in the common duct; (2) early cirrhosis secondary to the cholecystic disease; (3) an independent condition, or (4) cholecystitis secondary to a long-standing hepatic disorder. There was nothing in the history to indicate ductal obstruction. It is well

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known that varying degrees of dye retention may be observed with attacks of acute cholecystitis or even after biliary colic. This, however, is usually a transitory phenomenon. In this case, there was no such recent attack and the dye retention would seem indicative of some chronic disorder of the liver. Even with this finding it was impossible to correlate the patient's symptoms either with the cholelithiasis or the hepatic disorder. There was no suggestion in the history of any extraneous toxin and, clinically, we must assume some causal connection between the cholecystic disease and the disease of the liver.

The association of such hepatic disorders with cholecystic disease is of sufficiently frequent occurrence to be suspected more frequently and it should receive due consideration if surgical procedures are anticipated and probably should be a factor in urging such therapy. However, it is well known that surgical procedures for cholecystic disease in the presence of cirrhosis are accompanied by great risk, often accomplish little and, not infrequently, result disastrously. Whether surgery should be undertaken in such cases depends on various factors, including the general condition of the patient, the amount of distress the gallstones are producing and the evidence of significant progression of disease of the liver in which cases tests for liver function give considerable aid.

#### ATROPHY ASSOCIATED WITH SYPHILIS OR WITH ITS TREATMENT

*Case 2.* A woman, aged 40 years, was seen repeatedly at the clinic from 1928 to the present time. On her first visit she complained of a combined deafness of seven years' duration. The liver was slightly enlarged, the edge being two fingers-breadth below the right costal margin. The serology of the blood and spinal fluid was positive for syphilis. A diagnosis of late syphilis of the central nervous system was made. Treatment was instituted and was carried out faithfully. She was seen during the subsequent years for other conditions. In September 1934, the Kline test was 1+, the Kahn 1+, the Hinton positive and the Wassermann (Kolmer modification) negative. The Wassermann reaction of the spinal fluid was negative, the Nonne reaction was negative, one lymphocyte was present and the colloidal gold curve was 000,000,211,000,000. Treatment was not given between 1934 and 1936.

In January 1936, she returned because of progressive indigestion of three weeks' duration characterized by impaired appetite, epigastric fullness, distress after meals, belching, nausea, occasional emesis and loss of strength. On examination, there was some tenderness in the epigastrium, the liver extended three to four fingers-breadth below the costal arch and the spleen was palpable. The Kline test was  $\pm$ , the Kahn 2+, the Hinton positive and the Kolmer negative. The number of erythrocytes and the concentration of hemoglobin were normal. Macrocytosis was not present. Roentgenologic examination of the gall-bladder and stomach gave negative results. The bromsulphalein test indicated retention, graded 4. The van den Bergh reaction was direct. During the subsequent few months, the bromsulphalein retention decreased to grade 3, later to grade 1 and finally to 0. The van den Bergh reaction rapidly became normal. She was placed on a high carbohydrate diet, sodium phosphate was given before breakfast and occasional doses of calomel, mercury with chalk and a little potassium iodide were administered. On February 25, she reported that she was improved. In April, she appeared and felt much better. She progressed to complete recovery.

This patient had syphilis and some enlargement of the liver for a number of years. The syphilis had been treated adequately. The acute digestive symptoms of anorexia, nausea, vomiting and indigestion were very suggestive of hepatic disease and tests of liver function showed definite changes. Under therapy for disease of the liver she recovered. The hepatic disturbance could have been attributable to a recurrence of syphilis in the liver or to a toxic manifestation of the antisyphilitic treatment or to some unknown factor. The syphilologist is inclined too often to consider any development of a new condition in such a case as owing to the syphilis. Although such may be the case, there is reason to believe that some other factor may also be playing an etiologic rôle. The therapeutic test, furthermore, is not conclusive, as other factors, nonspecific in effect, may institute recovery, or the cessation of action of the toxic agent and the natural recuperative powers of the organism may be the chief factors at work. Relapse, as far as serology was concerned, did not occur in this case during this illness and the rate of recovery was more rapid than could be expected in a case of syphilitic hepatitis in view of the amount of mercury administered. The illness probably was not caused by latent toxic effects from previous therapeutic agents, as antisyphilitic drugs had not been given during the preceding two years. Neither was there a history of the use of other toxic agents such as cinchophen or alcohol, nor was there evidence of other systemic disease that would affect the liver. It is our opinion that the illness of this patient was an intercurrent hepatitis of unknown etiology.

#### ATROPHY OF EXOGENOUS TOXIC ORIGIN

*Case 3.* A man, aged 66 years, was examined at the clinic in July 1932. He had suffered from lumbago on three or four occasions in the previous 12 years. In the last four to five years constant lumbar pain with projection of the pain toward the posterior portion of both thighs had been present for which he had taken 170 to 190 tablets of cinchophen with considerable relief.

The edge of the liver was palpable 6 cm. below the costal margin; there was no evidence of ascites or of dilated collateral veins. The movements of the spine were limited. The concentration of bilirubin was 1.8 mg. in each 100 c.c. of serum and the van den Bergh reaction was indirect. The bromsulphalein test of liver function revealed retention of dye, grade 3. The galactose tolerance test gave negative results. The findings on cholecystographic examination were normal. Evidence of hypertrophic changes in the lumbar spine was found on roentgenologic examination. In November 1932, the liver was definitely decreased in size, its surface was smooth and its edge was soft. The degree of retention of dye had diminished to grade 1, the concentration of bilirubin was 1.2 mg. per 100 c.c. of serum and the van den Bergh reaction was indirect. In October 1936, he still complained of pain in both hips, particularly after exercise. Abdominal examination revealed no abnormalities. Dye retention was now absent; the concentration of bilirubin was 1.4 mg. per 100 c.c. of serum and the van den Bergh reaction was indirect.

This patient undoubtedly suffered toxic atrophy or hepatic degeneration without symptoms, apparently owing to the ingestion of cinchophen. The enlargement of the liver and the history of the use of cinchophen led us to

study the liver function. He has made a complete recovery. Numerous similar cases have been encountered, chiefly patients who had gout. The question arises: Should further cinchophen be given to patients who have gout and have such evidence of hepatic injury? Cinchophen has been used with improvement of gout but if gout can be kept under control by dietary methods alone, cinchophen should not be given. However, if the gout is active and severe, cinchophen becomes almost a necessity. Our custom in such cases is to give cinchophen for two or three days each week, in conjunction with sodium bicarbonate and a high carbohydrate diet. Evidence of toxic symptoms or objective evidence, either by clinical or laboratory methods, of disturbance of the liver requires omission of the cinchophen. We have not encountered difficulties by this procedure. Toxic symptoms include anorexia, nausea, epigastric distress, or other gastrointestinal symptoms. Urticaria or other signs of intolerance should not be ignored. If jaundice develops the drug should be discontinued at once.

Cinchophen is only one of many chemicals which may injure the liver. Numerous other drugs have at times a well recognized hepatotoxic effect, such as arsenic, chloroform, carbon tetrachloride, alcohol and phosphorus. In intoxications from these drugs, jaundice may occur in the more severe stages. The practical point is that patients receiving drugs which are known to produce hepatic injury at times, should be observed carefully and proper adjustments should be made if such disturbances develop.

#### ATROPHY UNASSOCIATED WITH OTHER DISEASES

*Case 4.* A man, aged 32 years, son of the patient whose case was reported first in this series, was seen at the clinic in July 1935. Ten years previously he had experienced painless icterus of two weeks' duration, associated with a digestive upset. Since then he has had spells of indigestion lasting from five to seven days and occurring every three or four months, increasing in frequency to the extent of having an attack every one or two weeks. These were characterized by impaired appetite, epigastric distress after eating, sour stomach, belching, constipation, light-colored stools, nausea, headaches, bad taste, sallow color and loss of weight. He felt generally miserable. He had weighed 152 pounds previously but had lost 15 pounds in the three months preceding registration at the clinic. He was an asthenic individual of sallow color. There was slight enlargement of the liver. A cholecystogram revealed a normally functioning gall-bladder. The bromsulphalein test of liver function revealed retention grade 1. The van den Bergh reaction was indirect and the concentration of bilirubin was 1.0 mg. per 100 c.c. of serum. The galactose tolerance test was normal. The Takata-Ara test was strongly positive. The albumin-globulin ratio and the values for serum protein, blood cholesterol and cholesterol esters were normal. Exploration was considered advisable. The appendix was removed. The gall-bladder was normal on inspection and palpation but when removed, it was found to contain a few small papillomata. The stomach, duodenum and pancreas were normal. The consistency of the liver was increased. A fine type of reticular fibrosis could be seen through the capsule. The characteristic irregularity of cirrhosis was not present.

There are several points of interest in this case: (1) the possibility of an inherited tendency to have hepatic disease; (2) the attacks of anorexia,

nausea, indigestion and light-colored stools, which readily could be considered functional in origin, should suggest the possibility of early hepatic disease; (3) in spite of a relatively long history and the appearance of the liver at exploration indicating definite anatomic evidence of injury, hepatic functional tests showed a minimum of abnormal findings and (4) the prognosis in these cases as a rule is not good, the condition often slowly progressing to a definite cirrhosis.

*Case 5.* A woman, aged 50 years, was seen in August 1937. She had had painless jaundice at the age of 12 years, since which time she had suffered from migraine headaches. In the five years preceding admission, the headaches had become progressively less frequent but she suffered attacks of restlessness, insomnia, anorexia, bloating, belching, aching and soreness in the right upper quadrant of the abdomen and light-colored stools. Her color was sallow and there was a history of loss of weight. She had not experienced chills, fever or colic. In December 1936 and in April 1937, she suffered more severe attacks and during the latter one, lost 15 pounds. Physical examination showed no significant abnormalities. The liver and spleen were not enlarged. The concentration of hemoglobin and the number and fragility of the erythrocytes were normal. Macrocytosis was not present. On cholecystographic examination a normally functioning gall-bladder was found. The bromsulphalein test of liver function revealed retention, grade 1. The van den Bergh reaction was direct and the concentration of bilirubin was 1.3 mg. per 100 c.c. of serum. Exploration was advised. This was performed elsewhere and the surgeon reported that, on examination of the liver, gross evidence of cirrhosis was found. The gall-bladder was atrophic and the extrahepatic bile ducts were small. Stones were not found in the gall-bladder or ducts.

This case resembles the preceding case in many respects. The symptoms are similar and the laboratory findings are minimal. The symptoms had many aspects of a functional disturbance, being particularly suggestive of a syndrome of an irritable bowel as encountered among asthenic patients. If disturbance of liver function had not been discovered, such a diagnosis would have been likely. In spite of the long duration of symptoms, only very slight disturbance of liver function was demonstrable by laboratory procedures, and yet at operation there was evidence of gross changes in the liver.

The etiology in these two cases is unknown. This is illustrative of the statement of Osler in regard to many liver conditions: "The absence of an etiologic factor was a remarkable feature of the disease." The significance of the painless jaundice suffered by these patients in earlier years is uncertain. It may indicate an initial injury of the liver and the beginning of a slowly progressive lesion. If such is the case, these patients illustrate well the ideas which Bloomfield<sup>1</sup> recently has expressed.

The last two cases were of a chronic nature and their symptoms were suggestive of disease of the liver. However, physical examination did not reveal enlargement of the liver or spleen. The following two cases are examples of acute mild injury, without symptoms that could be definitely attributed to the liver. The patients enjoyed good health.

*Case 6.* A man, aged 42 years, on routine examination in February 1933, was found to have slight enlargement of the liver. He did not have abdominal complaints. Laboratory tests were normal, including the van den Bergh reaction and concentration of bilirubin. The following year at his routine examination, a bromsulphalein test for liver function revealed retention, grade 2. On cholecystographic examination a normally functioning organ was found. In April 1935, he complained of exhaustion from overwork. The liver and spleen were slightly enlarged. Bromsulphalein retention was grade 1. The concentration of bilirubin was 1.4 mg. per 100 c.c. of serum. The van den Bergh reaction was indirect. The results of other tests were normal. In December 1936, he was enjoying good health and the results of all laboratory tests were normal.

*Case 7.* A man, aged 49 years, was examined in March 1936, at which time he complained of a slight sense of fullness in the right upper portion of the abdomen of about seven years' duration, relief from which was obtained by evacuation of the bowel. He had known that his liver was slightly enlarged during this time. Bromsulphalein retention was grade 2. The van den Bergh reaction was direct and the concentration of bilirubin was 1.4 mg. per 100 c.c. of serum. Macrocytosis was not present. The results of the hippuric acid test for liver function were normal as well as the content of serum protein and the albumin-globulin ratio. Roentgenologic examinations of the gall-bladder and stomach revealed no abnormalities. A month later, repetition of the test of liver function showed a dye retention, grade 3. He was seen again in February 1937, at which time he had no subjective symptoms. The edge of the liver extended 1 inch below the right costal margin. Bromsulphalein retention was grade 1. The results of other tests, including those of the van den Bergh reaction, were normal.

The slight enlargement of the liver found on physical examination in these cases stimulated further investigation of its function. Functional studies revealed a retention of bromsulphalein of varying degrees and alteration of the van den Bergh reaction, although other functional tests that were carried out were normal. These patients have been followed from two to four years. Subjectively they have been well, and functional studies now indicate little abnormality. The liver is still slightly enlarged, which, of itself, suggests some abnormality. However, the pathologic process does not at present appear progressive because of the improvement that has occurred. The finding of a functional disturbance at the time of their original observation, in spite of the absence of symptoms, probably indicates the presence of a mild acute or subacute toxic degeneration in a previously and mildly injured organ. The prognosis would appear to be good. A number of patients who had enlargement of the liver and who are without symptoms or demonstrable functional changes have been followed for many years without the occurrence of any symptoms or other signs of progression.

The following three cases represent a group of patients who experienced acute injury of the liver, of unknown etiology, associated with variable symptoms and followed by complete recovery.

*Case 8.* A woman, aged 49 years, was examined in March 1937. For many years she had vomited frequently and many operations had been performed elsewhere because of this symptom, without benefit. There was some evidence of congenital syphilis. Her nervous reactions were very unstable. For the 18 months preceding registration at the clinic, vomiting had been more severe. There had been varying

degrees of pain in the upper part of the abdomen. She had used morphine liberally. On examination she was emaciated and dehydrated. Hypochloremia (plasma chlorides 472 mg. per cent) was present but there was a normal concentration of urea and the carbon dioxide combining power was normal. The concentration of bilirubin was 2.5 mg. per 100 c.c. of serum and the van den Bergh reaction was direct. The bromsulphalein retention was grade 2. On administration of liberal amounts of dextrose and physiologic solution of sodium chloride intravenously, vomiting ceased, she felt and appeared much better, dehydration and hypochloremia were controlled and there was a disappearance of the direct van den Bergh reaction and bromsulphalein retention. Subsequently, she underwent exploration at which time the liver and biliary ducts appeared normal.

The relationship of the functional disturbance of the liver to the hypochloremia, dehydration and symptoms is uncertain. Possibly starvation and dehydration had led to fatty degeneration of the liver which could readily aggravate the nausea and vomiting. Furthermore, the liver plays a definite rôle in the regulation of water, as emphasized by Jones and Eaton.<sup>2</sup> Hypochloremia apparently was owing to the loss of gastric secretion by vomiting and probably had no relation to the disturbances of the liver. Administration of dextrose and physiologic solution of sodium chloride readily corrected both conditions. Gross abnormalities of the liver were not noted at exploration. As the vomiting was considered to be probably of functional origin, the case illustrates the chemical changes caused by functional disorders of long duration as demonstrated by laboratory procedures.

*Case 9.* A woman, aged 63 years, was examined in January 1936, because of nervousness, vague abdominal symptoms, indigestion and constipation. She had been seen on various occasions in the previous 20 years on account of constipation and numerous neurogenic disturbances, but there were no abnormal findings. Examination now revealed slight enlargement and tenderness of the liver. Bromsulphalein retention was grade 3, the concentration of bilirubin was 1.2 mg. per 100 c.c. of serum and the van den Bergh reaction was indirect. Six months later her symptoms were similar. The liver was slightly smaller. Bromsulphalein retention, grade 1, was present. Other laboratory procedures gave normal results. In August 1937, she presented herself again, with similar symptoms. Physical examination and tests for liver function were all normal.

This patient on numerous occasions had presented herself with functional gastrointestinal symptoms. These were possibly somewhat worse at the time liver dysfunction was found. However, because of her neurogenic manifestations, it was uncertain whether there were any additional symptoms that could be attributed to the liver. The slight enlargement of the liver led us to investigate its function. Recovery was complete from the standpoint of laboratory tests. No clues as to the etiology of the hepatic disorder were obvious at any time. The consistency of the liver did not suggest a chronic lesion. Any symptoms attributable to the disorder were obviously mild and, with the rapid recovery and decrease in size of the liver and normal functional tests, the prognosis would appear good.

*Case 10.* A man, aged 34 years, was seen repeatedly between 1932 and 1934, for a duodenal ulcer and sinusitis. In March 1934, a resection of the stomach was

done with excellent results. The liver was grossly normal. In December 1936, he returned because of nervousness, insomnia and periumbilical, abdominal distress of two months' duration. This was associated with anorexia, considerable nausea and a loss of 10 pounds in weight. Physical examination revealed no abnormalities. A faint trace of bile was found in the urine. The number of erythrocytes and the concentration of hemoglobin were normal. Macrocytosis was not present. On cholecystographic examination nothing abnormal was found. Bromsulphalein retention was grade 4, the van den Bergh reaction was direct and the concentration of bilirubin was 1.6 mg. per 100 c.c. of serum. As the result of a high carbohydrate diet and daily injections of dextrose intravenously he showed gradual improvement subjectively and, from a laboratory standpoint, the bromsulphalein retention was grade 3, grade 2 and subsequently, grade 1 during the two weeks after his admission. The van den Bergh reaction remained direct during this time. The elapse of another four weeks was necessary before he recovered. On examination a year later, he was in good health.

This patient's symptoms were acute and rather severe. In the history there was no suggestion of an etiologic factor. The severity of the symptoms and the degree of functional disturbance revealed by the results of various laboratory procedures indicate the presence of a rather severe hepatic injury. Improvement in the laboratory findings coincided with the clinical improvement. The normal condition of the liver at previous exploration and the recovery would indicate the presence of an acute hepatic injury with a favorable prognosis. The case is important in illustrating the necessity for considering such lesions in the explanation of unexplained sudden anorexia and nausea. This case corresponds in many respects to case 2, discussed previously under "Atrophy associated with syphilis or with its treatment" in this paper.

It is well recognized that the liver frequently is affected, without the production of jaundice, during the course of numerous infectious diseases, such as pneumonia, typhoid, malaria, septicemia, rheumatic fever and brucellosis, in which pathologic changes such as cloudy swelling, fatty degeneration or varying degrees of necrosis may occur. The involvement of the liver in cardiac decompensation, gummatous, metastatic and leukemic infiltrations, splenic anemia, exophthalmic goiter, eclampsia, amyloidosis, injuries from arsphenamine and alcohol is frequently unassociated with icterus. Weir and Comfort<sup>3</sup> have reported cases of toxic hepatitis from cinchophen without jaundice. More recently, Snell and Comfort<sup>4</sup> have described cases in which hepatic lesions were associated with extreme atrophy of the pancreas. Jaundice was not present in these cases. Furthermore, an occasional case of fatal acute yellow atrophy of the liver without jaundice has been reported such as that of Wilson and Goodpasture.<sup>5</sup>

The majority of the conditions discussed in the preceding paragraph are more or less well recognized. These conditions either with or without jaundice never have been classified satisfactorily from an etiologic, clinical, or pathologic standpoint and the attempt has not been made to so classify the cases presented in this paper.

In this group of cases the etiology is unknown. Evidence of the

presence of any other known hepatic toxins was not discovered. Jaundice was not present to call attention to the possibility of disease of the liver. In some cases, slight enlargement of the liver was present. In others, indefinite or extremely mild symptoms were present and the laboratory investigation was a more or less empirical procedure in an effort to find some organic explanation of the patients' complaints. The symptoms varied in severity. The sudden appearance of anorexia, nausea, occasional emesis, and epigastric distress, not otherwise explained, should direct attention toward possible disease of the liver. In milder cases, definite active therapy was not indicated. However, subsequent avoidance of substances known to have a toxic effect on the liver should be counselled. In the more severe cases, more active therapy is needed. The standard high carbohydrate diet, supplemented by intravenous dextrose, when necessary, proved adequate in this group of cases.

The pathologic changes are conjectural. Material obtained at necropsy or for biopsy is not available for study. Presumably the changes are degenerative processes, cloudy swelling, fatty degeneration or even some degree of necrosis involving the hepatic cells. The term "atrophy" employed in this paper has been used in a general way to indicate these various diffuse processes. The prognosis is likewise uncertain. Only time will decide this. Patients who have some enlargement of the liver probably have some underlying changes of a more chronic nature and the exacerbation is superimposed at the time of observation. Such exacerbations may occur on varying subsequent occasions and indicate the presence of a more or less progressive process and possibly give rise to other evidence of an extensive and irreparable hepatic disorder. However, in other instances, there is every reason to believe that the episodes encountered were acute, although of varying degrees of severity, that recovery occurred and that the future good health of the patient seemed probable.

#### SUMMARY

Extensive damage of the liver may occur under a variety of circumstances without jaundice or other symptoms or signs suggesting hepatic involvement. In such cases, diagnosis must rest largely on suspicion and the employment of tests of liver function. These disorders may be associated with diseases of the gall-bladder and biliary tract, or with syphilis and antisyphilitic therapy, or may result from the ingestion of exogenous toxins. There are many cases, however, unassociated with other diseases, in which the etiologic factor cannot be discovered. These conditions may be chronic or acute in nature and may or may not give rise to symptoms. In the chronic cases, symptoms include recurring mild indigestion, anorexia, nausea, constipation, headaches, weakness and malaise. The symptoms in the acute conditions are chiefly anorexia, nausea, vomiting, loss of weight and strength, and epigastric discomfort. Physical examination seldom reveals

any findings of significance. Qualitative alteration of the van den Bergh reaction and retention of bromsulphalein are the principal evidences of hepatic disorders from the standpoint of laboratory investigation. A group of cases illustrative of the above facts has been presented.

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# THE ACTION OF PARAHYDROXYPHENYLISOPROPYLAMINE (PAREDRI-NE) ON THE HEART; A CLINICAL STUDY OF A NEW EPINEPHRINE-LIKE COMPOUND \*

By MORRIS H. NATHANSON, M.D., F.A.C.P., *Los Angeles, California*

IT is well established that epinephrine is the most valuable therapeutic agent in the prevention and treatment of cardiac standstill. More recently the more stable compound, ephedrine, has been used in the treatment of the Adams-Stokes syndrome. The action of this drug in increasing ventricular excitability is variable and at times minimal, so that consistent results are not obtained and many therapeutic failures have been reported. In previous studies on the effect of drugs on the cardiac standstill induced by pressure on the carotid sinus,<sup>1</sup> it was found that the standstill could be prevented by a large group of substances related in chemical structure to epinephrine, while substances unrelated in structure were without effect. The intensity of the action increased as the chemical structure of the compound approached that of epinephrine. Ephedrine was the only substance available in these previous studies which was effective when administered by mouth. Ephedrine, however, possesses two features which limit its therapeutic value: (1) the comparative weakness of its action (ratio to epinephrine by this method 1:2000); (2) unpleasant side actions due to central nervous stimulation when administered in adequate dosage. It was concluded from the previous study<sup>1</sup> that further progress in the therapy of cardiac standstill lay in the direction of the development of stable epinephrine-like compounds having a more intense action than ephedrine.

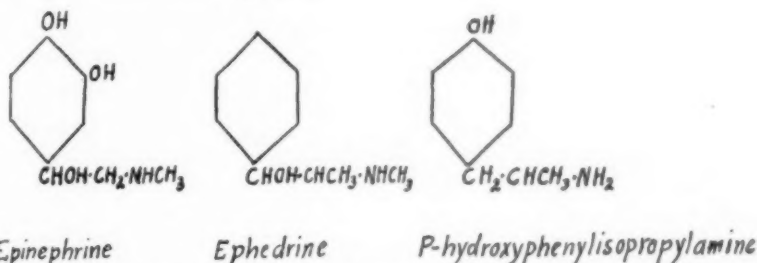


FIG. 1. Chemical structure of epinephrine, ephedrine and parahydroxyphenylisopropylamine (paredrine). (Reprinted by permission from Proc. Soc. Exper. Biol. and Med.)

Paredrine (the name which has been applied to parahydroxyphenylisopropylamine) stands between epinephrine and ephedrine in chemical structure (figure 1). On the basis of chemical structure this substance should

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have a more intense action than ephedrine since it is more closely related to epinephrine. Alles and Prinzmetal<sup>2</sup> have shown that paredrine has a more intense pressor action than phenylisopropylamine. Abbott and Henry<sup>3</sup> concluded that paredrine is about twice as potent as ephedrine in raising blood pressure. In contrast to the hydroxyamines (tyramine, hordenine, the synephrines) previously studied on cardiac standstill by Nathanson,<sup>1</sup> paredrine is effective on oral administration. In the present investigation the action of the drug was studied in three ways: (1) the effect on induced cardiac standstill; (2) the action in heart block; and (3) the modification of the ventricular complex of the electrocardiogram.







#### THE EFFECT ON INDUCED CARDIAC STANDSTILL

*Method.* The method utilized has been described in previous publications<sup>1</sup> but will be reviewed here briefly. It depends on the fact that it is possible in many individuals, especially elderly males, to induce a prolonged cardiac standstill by pressure on the right carotid sinus. Pressure on the carotid sinus produces an intense stimulation of the vagus in these subjects and the cardiac standstill is due to a temporary inactivity of the normal cardiac pacemaker—the sinus node, and to a failure of development of secondary centers of impulse initiation. The indication that a drug increases cardiac excitability is demonstrated by the prevention of the cardiac standstill due to the development of an impulse initiating center during carotid sinus stimulation. The rate of the new rhythm is the measure of the intensity of the effect and in this way the comparative actions of various compounds may be studied. Figure 2 shows the comparative activities of a group of epinephrine-like substances studied by this method.

Paredrine-hydrobromide\* was administered by mouth in 14 individuals in whom cardiac standstill could be consistently induced by pressure on the right carotid sinus. In each instance the following procedure was carried out. A control electrocardiogram was made showing the induced cardiac arrest. A single dose of the drug was then administered by mouth which consisted in 12 instances of 60 mg., and in two cases of 40 mg. Electrocardiograms were then taken at intervals and pressure on the carotid sinus repeated. The cardiac standstill was modified in every case. The effect was noticed in 12 cases within 30 minutes after the oral administration of the drug; in two instances the action was not observed until one hour had elapsed. The standstill was abolished in seven individuals by the development of a rhythm, arising in or near the auriculo-ventricular node. In three cases lower ventricular centers became active. In one the rhythm consisted of beats arising from the sinus node alternating with beats arising from an ectopic ventricular focus, while in three instances the sinus node retained its activity. In four subjects the experiment was repeated after an interval of several days or a week, using 100 mg. of ephedrine sulphate. In one

\* The paredrine-hydrobromide was supplied by Smith, Kline and French Laboratories of Philadelphia.

patient 100 mg. of ephedrine sulphate failed to show any effect on the induced cardiac standstill, while 60 mg. of paredrine hydrobromide definitely abolished the standstill (figures 3 and 4). In three instances ephedrine pro-

Drug	Structural Formula	Approximate Ratio of Activity to 1-epinephrine
1-epinephrine		1:1
d-epinephrine		1:20
α-hydroxy Δ-amino 3,4 dihydroxy propyl- benzene		1:10
Synthetic Substance		1:40
Synthetic Substance		1:40
Neosynephrin hydrochloride		1:100
Synephrin tartrate		1:400
Tyramine		1:1,200
Hordenine		1:6,000
Ephedrine		1:2,500 - 1:2,000
Phenylethanolamine		1:8,000
Catechol		Ineffective

The compounds were in the following forms: 1-epinephrine, α-hydroxy Δ-amino 3,4 dihydroxy propylbenzene and the first-mentioned "Synthetic Substance" as hydrochlorides; d-epinephrine as the bitartrate; tyramine and hordenine, ephedrine and phenylethanolamine as the sulphates.

FIG. 2. Comparative activities of epinephrine and related compounds on induced cardiac standstill. (Reprinted by permission from Proc. Soc. Exper. Biol. and Med.)

duced qualitatively the same effect as paredrine but the reaction was definitely less intense, in that the effect of the paredrine was observed earlier and the duration was longer (figures 5 to 8). The qualitative similarity of the effect is indicated by the identical contours of the complexes of the beats which were induced by the two drugs. Of special interest was the fact that symptoms which may be attributed to central nervous stimulation were not seen following paredrine. Symptoms such as nervousness, tremor or apprehension were looked for, but were not observed in any case. Headache

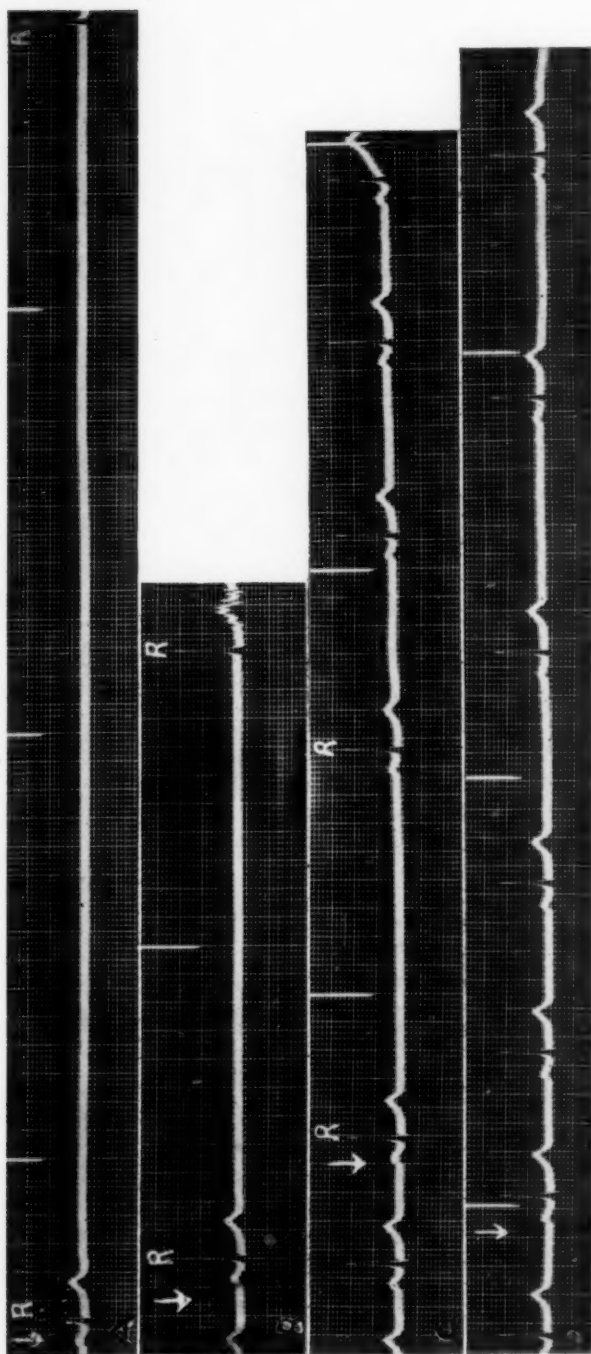


FIG. 3. (Patient B. G.) Strip A shows cardiac standstill of 9 seconds induced by pressure on the right carotid sinus (arrow). Strip B taken 30 minutes after the oral administration of 60 mg. of parendrine hydrobromide, the standstill reduced to 4.4 seconds. C and D taken 60 and 90 minutes after the administration of parendrine. Carotid sinus pressure (arrow) produces only a moderate slowing of the heart.

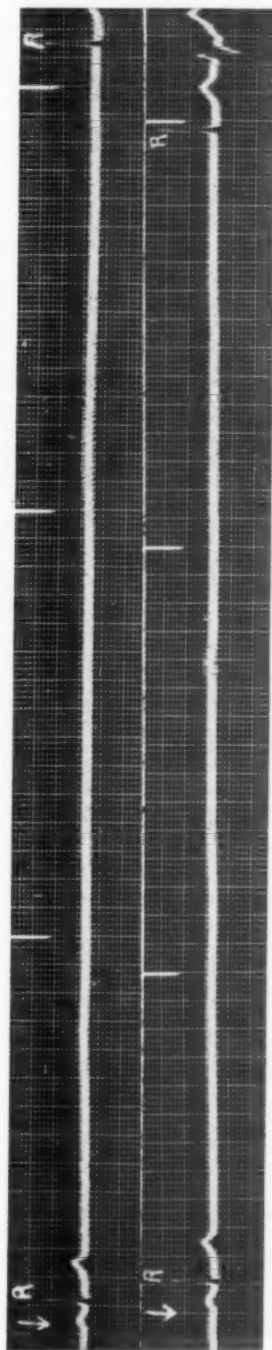


FIG. 4. (Patient B. G.) Upper strip shows cardiac standstill of 8.8 seconds induced by pressure on the right carotid sinus (arrow). After 100 mg. of ephedrine sulphate the cardiac standstill could be reproduced consistently. Lower strip shows the standstill induced 1 hour after the administration of 100 mg. of ephedrine sulphate.

of moderate severity was noted in two patients and this was promptly relieved by the sub-lingual administration of nitroglycerine.

#### EFFECT ON HEART BLOCK

Experimental and clinical studies indicate a variable effect of epinephrine in heart block. There is usually a rise in the ventricular rate in complete



FIG. 5. (Patient G. S.) Strip A shows cardiac standstill of 7.2 seconds induced by pressure on the right carotid sinus (arrow). Lower strips taken at 15-minute intervals following the oral administration of 60 mg. of parahydroxyphenylisopropylamine hydrobromide. Strips C and D show the standstill prevented by the development of beats of auricular and ventricular origin. In strip E the beats are all supraventricular in origin. (Reprinted by permission from Proc. Soc. Exper. Biol. and Med.)

heart block, but this is not constant. The effect on the block is variable. At times there is a lessening or disappearance in the conduction defect but in most instances the block is unaffected. Cullis and Tribe<sup>4</sup> showed that epinephrine increases the ventricular rate both before and after section of the auriculoventricular bundle. Routier<sup>5</sup> produced complete heart block in dogs by crushing the auriculo-ventricular bundle. He then injected  $\frac{1}{20}$  mg. of epinephrine intravenously. The first effect was an acceleration of both chambers, the secondary effect was entire disappearance of the block. Danielopolu and Danulescu<sup>6</sup> in a case of partial block (2:1), reduced the block with epinephrine 1.5 mg. subcutaneously so that only an occasional beat was dropped. Hardoy and Houssay<sup>7</sup> reported a case of complete heart block in which 1 mg. of epinephrine subcutaneously had no effect on the

block or on the heart rate. The same dose intravenously resulted in great acceleration of both auricular and ventricular rates, but no change in the block. Phear and Parkinson<sup>8</sup> reported a case of complete heart block in which epinephrine abolished the syncopal seizures although the block was unaffected and the ventricular rate was not accelerated. Parkinson and

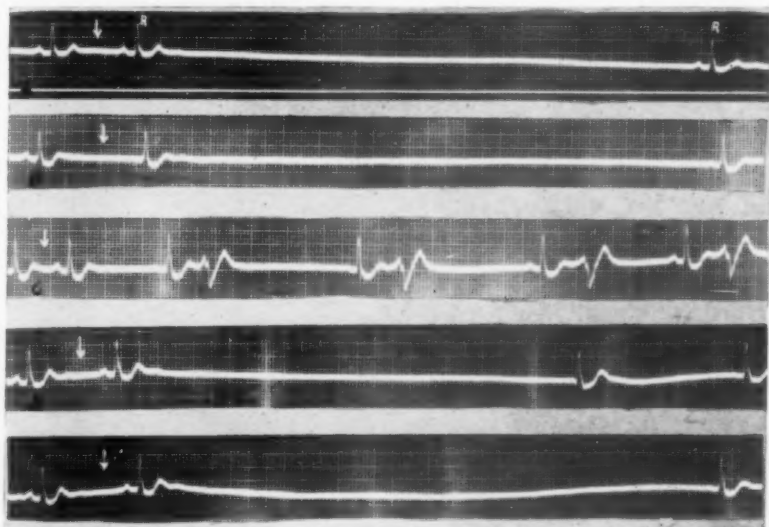


FIG. 6. (Patient G. S.) Strip A shows a cardiac standstill of 7 seconds induced by pressure on the right carotid sinus (arrow). Strip B taken 30 minutes after the oral administration of 100 mg. of ephedrine sulphate. The cardiac standstill can still be induced. Strip C taken 45 minutes after the drug shows the standstill prevented by the development of beats of auricular origin alternating with beats of ventricular origin. D and E taken at 60 and 75 minutes after the drug show the disappearance of the effect. Compare with figure 5 and note that the response to the ephedrine is qualitatively similar but distinctly less intense. (Reprinted by permission from Proc. Soc. Exper. Biol. and Med.)

Bain<sup>9</sup> also reported the disappearance of syncopal seizures but the effect of repeated administration on the same patient was variable. On one occasion there was an increase in the ventricular rate while at another time the rate remained unchanged. When partial block was present in this individual, epinephrine produced an increase in the rate of both auricles and ventricles, and finally restoration of normal rhythm. Feil<sup>10</sup> completely abolished syncopal attacks in a patient suffering from complete heart block by the subcutaneous injection of 0.6 mg. of epinephrine. The block was not influenced and there was only a slight increase in ventricular rate from 29 to 31 a minute. These reports indicate that epinephrine may have the following effects in auriculo-ventricular block: (1) the ventricular rate may be increased and the block remain unaffected; (2) there may be a variable degree of lessening of the block; (3) beneficial effects as indicated by the prevention of syncopal attacks may occur without acceleration of the ventricular rate or the modification of the block. In the present study the effect of the

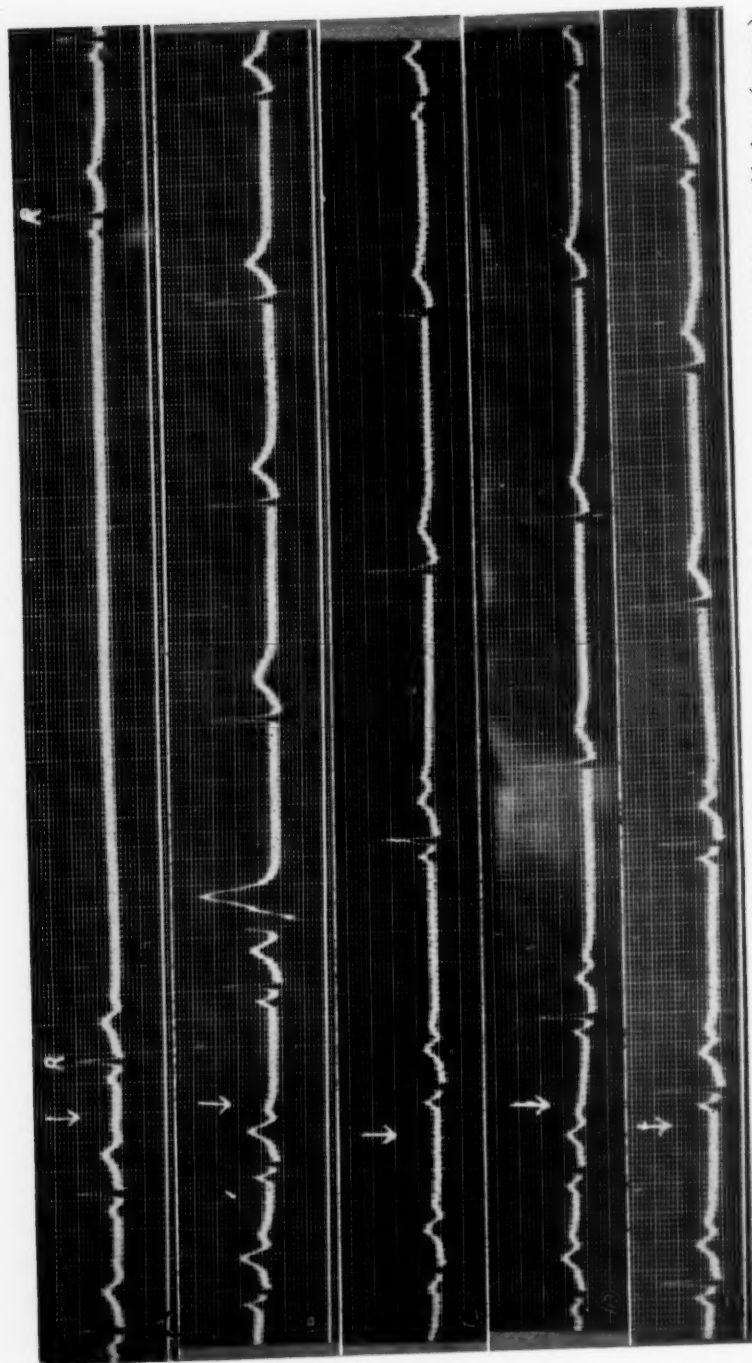


FIG. 7. (Patient J. B.) Strip A shows cardiac standstill of 6 seconds induced by pressure on the right carotid sinus (arrow). Strips B, C, D and E were taken 30, 60, 75 and 90 minutes after the oral administration of 60 mg. of paredrine hydrobromide. Pressure on the carotid sinus is now followed by a nodal rhythm, average rate 38 per minute.

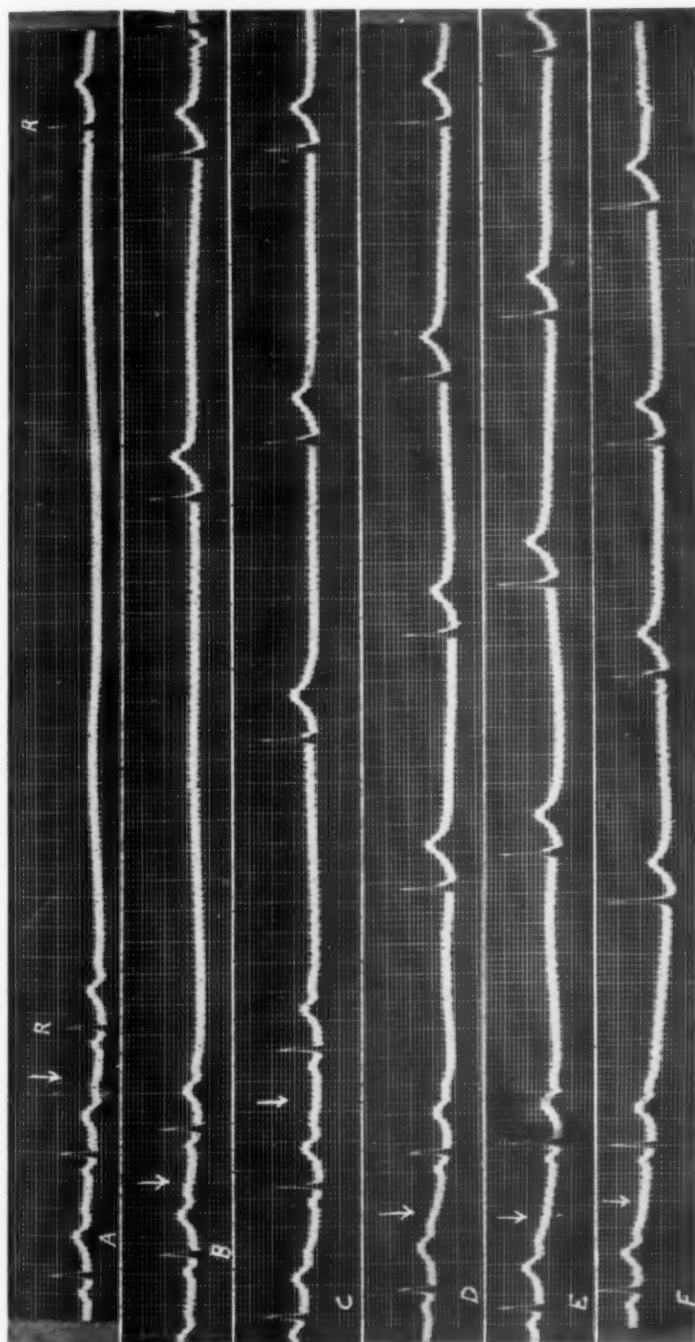


FIG. 8. (Patient J. B.) Strip A shows cardiac standstill of 6.2 seconds induced by pressure on the right carotid sinus. Strip B, taken 30 minutes after the oral administration of 100 mg. of ephedrine sulphate, still shows a standstill of 4 seconds (compare with figure 7B). Strips C, D, E and F were taken 45, 60, 75 and 90 minutes after the drug and show that pressure on the carotid sinus is followed by a nodal rhythm, average rate 33 per minute.

oral administration of paredrine was observed in six cases of heart block. In four there was complete auriculo-ventricular dissociation and in two instances the block was partial. The following is a summary of these cases:

*Case 1.* Patient T. B. Complete block. Auricular rate 80 per minute, ventricular rate 43.4 per minute. Thirty minutes after 60 mg. of paredrine hydrobromide by mouth the auricular rate was 80, the ventricular rate 44.8. At one hour, and at 90 minutes, the auricular rate was 80 and the ventricular rate was 48.4. At two hours, the ventricular rate was reduced to the original level, 43.4 beats per minute. The block remained complete throughout.

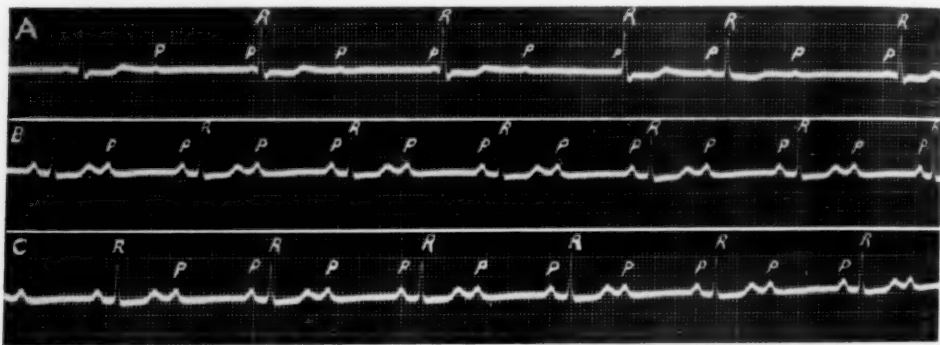


FIG. 9. (Patient M. H.) Strip A shows complete heart block, auricular rate 70 per minute, ventricular rate 34. Strips B and C were taken 60 and 90 minutes after the oral administration of 60 mg. of paredrine hydrobromide. The block is now partial (2 to 1), auricular rate 84, ventricular rate 42. Note increase in amplitude in P-wave in strips B and C.

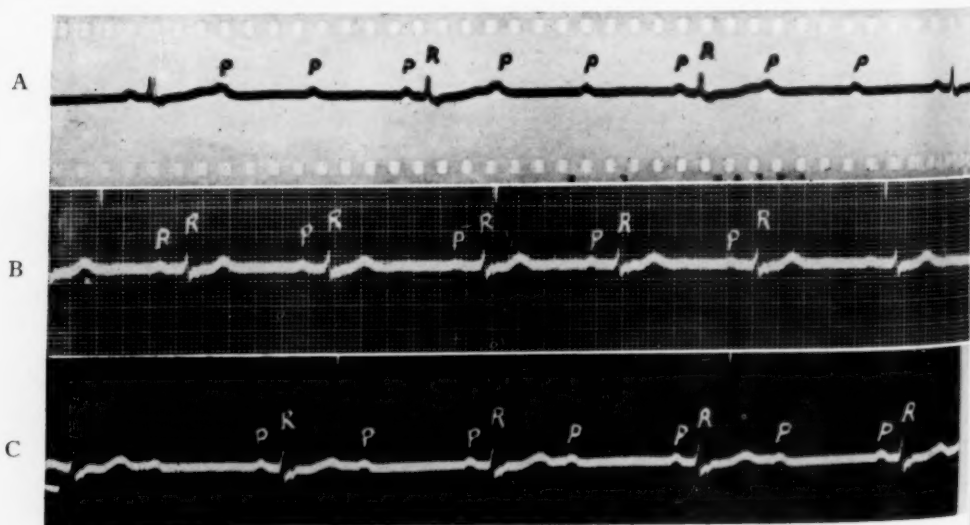


FIG. 10. (Patient J. C.) Strip A shows partial (3 to 1) block, auricular rate 90, ventricular rate 30. Strip B shows the disappearance of the block after the administration of paredrine hydrobromide 60 mg. three times a day for a week. The drug was discontinued for a week and strip C shows return of block (2 to 1) at this time.

Time		Rate	
		Auricular	Ventricular
1:05	Paredrine 60 mg.	78	30
1:35			30
1:50		64	30
2:05		82	46
2:15		90	48
2:25		82	46
2:40		88	46
3:00		84	54

FIG. 11. (Patient M. W.) Complete heart block, showing the effect on the auricular and ventricular rates of 60 mg. of paredrine hydrobromide by mouth.

*Case 2.* Patient M. H. Complete block. Auricular rate 70 per minute, ventricular rate 34 per minute. Sixty minutes after the administration of 60 mg. of paredrine hydrobromide by mouth the mechanism was partial block, 2: 1, auricular rate 84, ventricular rate 42. This effect still persisted at 90 minutes when the observations were discontinued. There was a definite increase in the amplitude of the P-wave in the electrocardiogram after the administration of the drug (figure 9).

*Case 3.* Patient J. C. Partial block, 3: 1, auricular rate 90, ventricular rate 30. In this patient a dose of 60 mg. was administered three times a day for one week. A record at this time showed the disappearance of the block with a ventricular rate of 58. The drug was then discontinued for a week. The record at this time showed a partial block, 2: 1, auricular rate 76, ventricular rate 38 (figure 10).

*Case 4.* Patient M. W. Complete block, auricular rate 78, ventricular rate 30. This patient had been counting his pulse for four years and the rate had never been

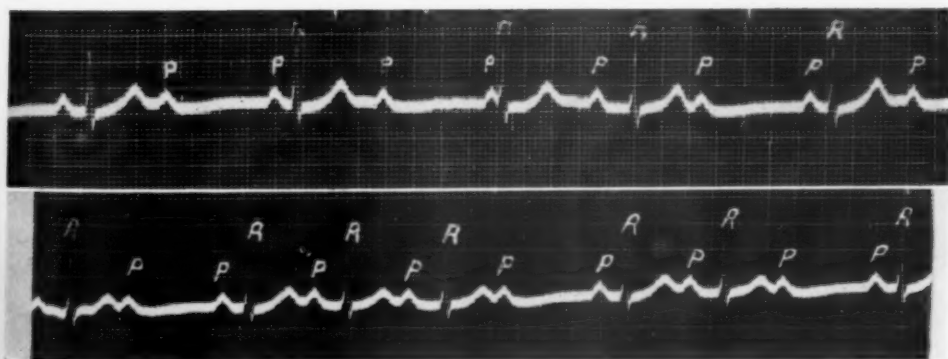


FIG. 12. (Patient J. K.) Upper strip shows complete heart block, auricular rate 82, ventricular rate 48. Lower strip taken 1 hour after the oral administration of 60 mg. of paredrine hydrobromide by mouth shows partial block with dropped beats, auricular rate 94, ventricular rate 66. This effect was reproduced on several occasions.

observed above 30 per minute. After 60 mg. of paredrine hydrobromide by mouth the ventricular rate rose to 46 a minute in 1 hour and to 54 per minute in 2 hours. This effect is shown in figure 11. The increase in ventricular rate was due chiefly to the development of ectopic ventricular beats.

*Case 5.* Patient W. L. Partial block. Auricular rate 64, ventricular rate 32. Paredrine hydrobromide 25 mg. was injected intravenously. In five minutes the

ventricular rate rose to 52 with ventricular beats arising from ectopic foci. At 10 minutes the basic ventricular rate was 36. The mechanism was the same at 30 minutes when the observation was completed.

*Case 6.* Patient J. K. Complete block with frequent syncopal attacks. Auricular rate 82, ventricular rate 48. One hour after 60 mg. of paredrine hydrobromide by mouth there was partial block with the predominant rhythm consisting of two cycles of 1:1 rhythm followed by one cycle of 2:1 block, auricular rate 94, ventricular rate 66 (figure 12). The same mechanism was present 90 minutes after the administration of the drug. Patient received 60 mg. of paredrine three times a day; after a period of two months reported that he had had no further syncopal attacks.

#### EFFECT ON THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM

The effect of epinephrine on the electrocardiogram has been studied in man as well as in animals. Various deviations have been induced by epinephrine but the most consistent alteration is in the T-wave and the R-T interval. Bartos and Burstein<sup>11</sup> noted inversion of the T-wave following

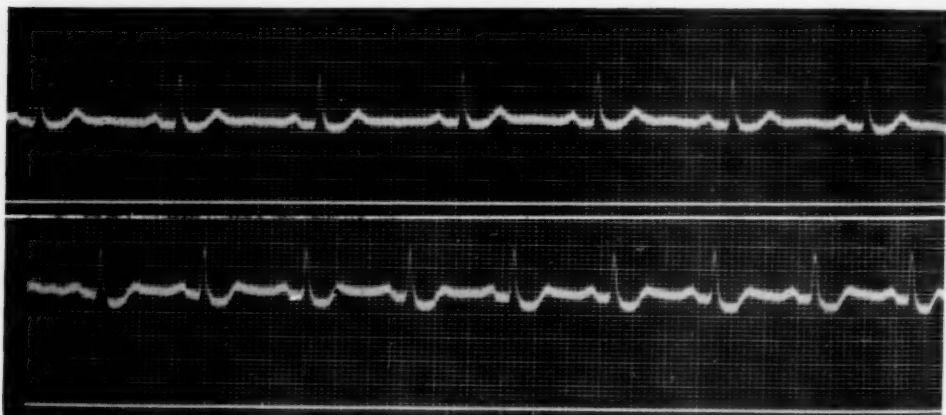


FIG. 13. (Patient G. S.) Upper strip is control record. Lower strip shows definite depression of the R-T segment 1 hour after the oral administration of 60 mg. of paredrine hydrobromide.

injection of 1 to 2 c.c. of a 1:100,000 solution of epinephrine. Katz<sup>12</sup> observed depression of the R-T interval and diminished amplitude of the T-wave following the administration of epinephrine in patients. In a study on the action of epinephrine on the human heart Nathanson<sup>13</sup> observed depression of the S-T and changes in amplitude of the T-wave. More recently, Milles and Smith<sup>14</sup> found that the minimal effect of epinephrine was reduction in the amplitude of the T-wave. Next, directional changes in the T-wave followed: a previously upright T became inverted or vice versa or a marked increase in voltage in the T-wave appeared. Deviation of the S-T interval from the isoelectric line was often associated with the T-wave alterations. Douglas<sup>15</sup> and his associates produced S-T changes resembling those of coronary occlusion by the administration of epinephrine to cats.

In the present study, modifications of the electrocardiogram were frequently observed after the oral administration of paredrine. Of 12 individuals in whom a dose of 60 mg. was administered, the R-T segment was depressed in four and slightly elevated in one instance. The T-wave was increased in amplitude in seven, and depressed in five. In two cases, the chest lead was studied following the administration of paredrine. In one instance the normally inverted T of the chest lead became more deeply inverted. In the other case the patient developed cardiac pain after the administration of 60 mg. of paredrine. The ventricular complex became monophasic, with marked elevation of the R-T segment, resembling the

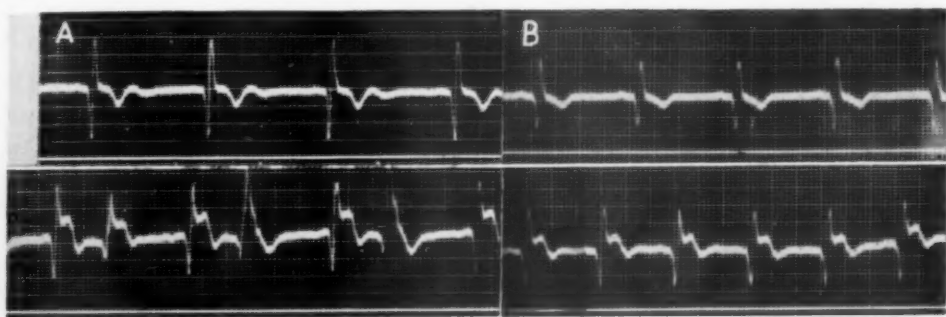


FIG. 14. (Patient G. S.) A, upper strip, control record of precordial lead (chest electrode over apex, indifferent electrode on left leg). Lower strip shows monophasic curve with marked elevation of R-T segment 1 hour after the oral administration of 60 mg. of paredrine hydrobromide. B, upper strip, control record of precordial lead. Lower strip shows the precordial electrocardiogram taken 1 hour after the oral administration of 100 mg. of ephedrine sulphate.

changes which follow acute coronary obstruction (figure 13). In a subsequent experiment 100 mg. of ephedrine sulphate by mouth produced a similar change in the electrocardiogram of this patient. The similarity in the modifications of the electrocardiogram following the administration of epinephrine and paredrine is further evidence of the epinephrine-like action of paredrine on the heart.

#### COMMENT

The results of this study indicate that paredrine exerts an epinephrine-like action on the heart. This is shown by the effect on induced cardiac standstill, by its action on heart block and by the modification of the ventricular complex of the electrocardiogram. The effect of paredrine is less intense but more prolonged than that of epinephrine. The chief advantage of paredrine lies in its stability so that the drug is effective on oral administration. The superiority over ephedrine is its greater intensity of action and the absence of unpleasant side effects. The therapeutic indication for paredrine in cardiac disease is therefore the same as for epinephrine and ephedrine, which is primarily the prevention and treatment of cardiac

standstill. In heart block associated with syncopal attacks a drug effective by mouth is frequently desirable. The present studies indicate that paredrine is the most active epinephrine-like compound for the purpose. A dose of 40 to 60 mg. three or four times a day appears to be sufficient to raise ventricular rhythmicity to a degree so that the tendency to ventricular standstill is definitely lessened. Another indication is the prevention of the asystole associated with the hypersensitive carotid sinus, a syndrome which has been described by Weiss and Baker.<sup>16</sup> Three of the 14 individuals of the present study in whom cardiac standstill could be induced suffered from spontaneous attacks of syncope and were relieved by the administration of the drug.

#### SUMMARY

1. Parahydroxyphenylisopropylamine (paredrine) is a drug related in chemical structure to epinephrine and ephedrine.
2. The substance is effective on oral administration.
3. Paredrine effectively prevents the cardiac standstill induced by pressure on the carotid sinus and is at least twice as effective as ephedrine in this action.
4. When administered in dosage effective in preventing cardiac standstill, paredrine does not produce unpleasant side effects due to central nervous stimulation.
5. Paredrine has an epinephrine-like action in auriculo-ventricular block.
6. Paredrine produces changes in the ventricular complex of the electrocardiogram similar to those which follow the administration of epinephrine.
7. Paredrine has certain advantages over epinephrine and ephedrine in the therapy of cardiac and ventricular standstill.

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## TOLERANCE AND TOXICITY OF INSULIN

### III. PROTAMINE AND ZINC COMPOUNDS\*

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COMPLETION of the desired range of experiments was prevented by circumstances. The material used was the regular preparation of protamine zinc insulin as supplied by Eli Lilly & Co. for clinical use. The results, though fragmentary, establish several new facts, as follows.

#### I. PROTAMINE INSULIN WITH SPONTANEOUS EATING

These observations were limited to rats. As mentioned in the previous paper, it has never been possible to produce extreme obesity in adult animals of any species with regular insulin. MacKay and Callaway<sup>1</sup> have recently reported the interesting discovery that this can be accomplished in rats with doses of about eight units of protamine insulin, given once or twice daily. The great and sustained increase of appetite is the remarkable feature in comparison with regular insulin.

The present work dealt only with brief experiments, usually with larger doses, and therefore this fattening effect was missed. Another difference as regards appetite was encountered, however, in the form of a failure of appetite with higher doses. Whereas average sized rats will continue to eat moist bread in sufficient quantities to keep themselves safe with doses of 300 to 1000 units of regular insulin, the tolerance for protamine insulin is far lower. With single doses of 10 to 20 units or more, if the rats are unwatched occasional ones are found dead, and this mortality increases as the doses are either increased or repeated from day to day. Although there have been no sufficiently thorough tests to establish a precise limit, it has not been feasible to give single injections as high as 50 or 60 units with spontaneous eating, because of loss of appetite. With lower doses the rats under continuous watch can be injected with glucose at the first sign of hypoglycemia; they will then sometimes resume eating and can be saved by a combination of feeding and occasional glucose injections. With doses of 50 units or sometimes less this combination seems to fail, and recourse must be had entirely to parenteral injections, the difficulties of which are described below.

#### II. PROTAMINE INSULIN AND PARENTERAL GLUCOSE INJECTIONS IN RATS

It was shown in the previous paper that fasting rats can tolerate above 100 units of regular insulin with the aid of subcutaneous glucose injections.

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From St. Michael's Hospital, Newark, New Jersey.

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It is therefore a surprise to find that an injection of 10 to 15 units of protamine insulin is fatal for an ordinary sized fasting rat; deaths may occur after as little as five units, and only exceptionally large rats (350 to 450 gm.) can survive as much as 20 units. A direct toxic effect of the insulinate here is excluded. The determining factor is the relentless persistence of the

TABLE I  
Rats—Protamine Insulin with Parenteral Glucose Administration

No. of Animals	Weight gm.	Prota- mine insulin units	Hours before 1st re- action	Glucose in 1st 12 hrs. gm.	Glucose in 2nd 12 hrs. gm.	Glucose for re- maining period gm.	Total glucose gm.	Total hours of treat- ment	Result
		Subcu- taneously							
3	120-180	5	2½-4	1.5-2.5	2.7-3	0 -9.8	5.2-14.3	24-53	2 lived, 1 died.
8	90-200	10	4½-8	1.4-2.8	2.0-3.3	5.2-7.4	6.8-13.1	50-58	Progressive weakness, dysp- nea, hydremia. Death.
5	140-250	15	3½-5	2.2-4.2	3.0-3.8	4.6-6.8	9.9-14.4	28-42	Same.
6	95-190	20	1½-4½	1.8-3.0	1.8-3.0	4.1-7.2	7.9-13.0	24-37	Same.
3	350-440	20	2-3	2-2.5	1.5-2	1.2-1.5	4.8-5.8	32-40	Weakness, subnormal tem- perature. Recovery.
3	120-190	30-40	2½-3½	1.5-2.7	2.8-3.8	3.0-7.6	7.1-13.8	38-57	Weakness, etc. Death.
3	110-195	50-60	3-4½	1.0-2.1	3.2-4.0	3.9-11.0	7.9-16.8	36-44	Same.
2	120-160	100	2-3½	1.6-3.1	2.8-4.2	3.3-6.8	8.2-14.0	34-48	Same.
2	125-200	150	1½-2½	2.5-3.0	4.5-5.8	6.2-10.8	12.8-19.0	32-45	Same.
		Intra- venously							
1	100	40	2½	1.5	0.5	—	2.0	15	Sudden death.
1	110	150	3½	3.0	1.6	0.3	4.9	25	Progressive weakness. Death.
1	135	300	2	2.5	2.1	2.5	7.1	40	Weakness progressing to death 15 hours after last injection. Autopsy blood sugar 160.

insulin activity, which continues until the glucose injections reach an amount which is fatal to any rat. Depending upon the individual strength and other variables, it is seen in the table that a dose of as little as 10 units may keep up its effect for as long as 58 hours. Many blood counts (not tabulated) have shown marked hydremia.

Though the duration is so much longer, the intensity of the action is not greatly different from that of ordinary insulin, as judged either by the interval before the first hypoglycemic attack, or after that by the hourly demand for injected glucose. There are some clinical reports which indicate that protamine insulin has a higher glucose equivalent than ordinary insulin. Since the conditions are exaggerated in animals, because of the much longer activity, there is a plainer demonstration that the essential difference is merely one of time. The fallacy of insulin-glucose ratios is thus further illustrated, because comparisons of both the total glucose equivalency of regular and protamine insulin and the hour-by-hour effect of small versus large protamine insulin doses are reduced to absurdity in these animal experiments.

The results of intravenous injections in only three animals must be viewed as suggestive rather than conclusive. The impression is conveyed that protamine insulin is more toxic than regular insulin, because a dose as

low as 40 units was fatal. This effect, however, can scarcely demonstrate a direct toxicity of the insulinate itself, since, by a peculiar accident, the survival with 300 units was longer than with smaller doses.

With reference to glucose metabolism, there seems to be the usual indication of inferior potency of insulin by the intravenous as compared with the subcutaneous route. Though all three animals died, they lived long enough to prove decisively (cf. previous paper) that protamine insulin has a more prolonged effect than regular insulin also with intravenous administration. This statement applies to large doses, which presumably cause a passage of some unchanged protamine insulin into the tissues, from which it may be absorbed gradually. The identical effects of regular and protamine insulin intravenously were obtained by Longwell and Ravin<sup>2</sup> with doses of only 1.5 units per kg. in rabbits. Similar differences prevail with subcutaneous dosage; the effects of large doses in human patients may last into the third day (Lawrence and Archer<sup>3</sup>; Sprague and Rynearson<sup>4</sup>), while the smallest doses show no difference from regular insulin (Patel and Rönmark<sup>5</sup>; Wilder and Wilbur<sup>6</sup>).

### III. ANTIDOTING BY COMBINED FEEDING AND GLUCOSE INJECTIONS

Some of the preceding remarks are further illustrated by table 2. It may be noticed that the rats could be saved after doses up to 40 units, but after 60 units or more all died.

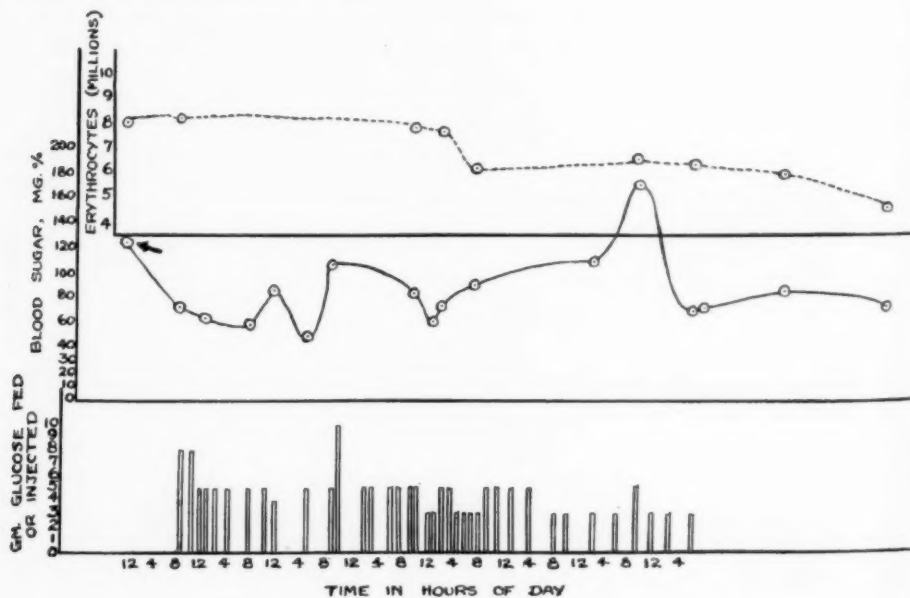


FIG. 1. Rat 401N; weight 215 gm. 15 units protamine insulin subcutaneously. Arrow shows time of injection.

The method of saving life consists in sparing the animals from the injury of too long continued parenteral glucose injections. Thus, by feeding

either bread or glucose for one or two days after the insulin injection, the survival period can be lengthened, and a separate record (figure 1) shows how a strong rat was saved in this way after 15 units of protamine insulin, which continued to cause hypoglycemic convulsions for 90 hours. Also, if appetite is retained, feeding may replace injections on some of the later days and the rat may thus survive. Rats 3, 4 and 5 in table 2 show how life may

TABLE II  
Rats—Subcutaneous Injections of Regular or Protamine Insulin;  
Carbohydrate Feeding; Glucose Injections

Rat No.	Weight gm.	Insulin dosage. Units	CH in 1st 24 hrs.		CH in 2nd 24 hrs.		CH in 3rd 24 hrs.		Total hrs. of treatment	Result
			Fed gm.	Glucose injected gm.	Fed gm.	Glucose injected gm.	Fed gm.	Glucose injected gm.		
1	215	15 P	5 bread	0	0	1.5	0	4.3	120	Glucose injections, 4.8 gm. in 4th 24 hrs., 2.0 in 5th 24 hrs. Progressive weakness. Death with normal blood sugar.
2	250	15 P	4 bread	0	3.2 glucose	0	2.0 glucose	1.8	124	Glucose injections, 3.6 gm. in 4th 24 hrs., 2.4 gm. in 5th 24 hrs., 1.0 gm. in last 4 hrs. Lived.
3	130	20 P	9 bread	0	5 bread	1.0	1.4 glucose	1.0	72	Moderate weakness. Fed ad libitum after 72 hrs. Lived.
4	150	20 P	8 bread	0	3.6 glucose	0	3 glucose	0	72	Fed ad libitum after 72 hrs. Lived.
5	150	40 P	12 bread	0	3 bread	3	—	—	48	Fed ad libitum after 48 hrs. Lived.
6	140	40 P	6 bread 2 glucose	0	4 bread	2	—	—	48	Food omitted after 48 hrs. Hypoglycemic death.
7	185	60 P	12 bread	0	6 bread	0.5	6 bread	0	72	Died in sudden unexpected hypoglycemic attack.
8	150	80 P	10 bread	0	7 bread	0	5 bread	1.2	72	Died in sudden convulsion, probably hypoglycemic.
9	100	2 × 40 P, 15 hr. intervals	0	5.6	0	4.2	0	1.0	54	Progressive weakness. Death.
10	135	3 × 10 P, 15 hr. intervals	11 bread	0	0	5.0	0	4.8	90	Glucose injections 4.0 gm. in last 18 hrs. Weakness. Death.
11	290 obese	3 × 20 P, 18 hr. intervals	0	0.9	0	4.5	0	4.1	114	No glucose required for first 12 hrs. Total injected 16.8 gm. Progressive weakness. Death.
12	140	3 × 150 regular insulin, 12 hr. intervals	15 bread	0	5 bread 2 glucose	2.0	—	—	36	Apparent recovery; sudden death at 48th hr.
13	170	8 × 100 regular insulin, 12 hr. intervals	16 bread	0	2.5 glucose	0	3.0	0	120	Glucose 2.4 gm. eaten in 4th 24 hr., 2.7 gm. injected in 5th 24 hr. Lived.

thus be saved after 48 or 72 hours, after doses as high as 20 or 40 units. But (rat 6) if both feeding and glucose injections are withheld after 48 hours, hypoglycemic death results.

With the largest doses this device fails to save life, because of the failure of appetite or strength, due apparently to a direct toxic action of the insulin independent of excess or deficiency of glucose. As above mentioned,

this effect is produced by much smaller doses of protamine insulin than of regular insulin.

Rats 9, 10 and 11 show how doses of 10 to 40 units of protamine insulin (which singly permit of survival, because appetite is retained) may become fatal when repeated two or three times at intervals of 15 to 18 hours. The rats could not be saved by feeding on the later days because they had lost appetite; therefore they succumbed to the continued glucose injections.

A comparison of insulin-glucose ratios (at least as obtained with the method in clinical use, namely subcutaneous insulin injections) may be made between rats 1 and 2, which received single injections of protamine insulin, and rat 13, which received 800 units of regular insulin divided into eight injections of 100 units each 12 hours apart. The duration of the hypoglycemic effect was practically identical in the three animals, namely 120 to 124 hours. Furthermore the total amount of carbohydrate required for antidoting the 800 units was not very greatly different from that required for the 15 units.

One of these three rats (number 11) furnished an example of exceptional individual tolerance (perhaps due to obesity) in that it could remain symptom-free for 12 hours after 20 units of protamine insulin, and required only 0.9 gm. of glucose for the rest of the 24 hours.

In respect to carbohydrate metabolism, the 800 units of regular insulin was very slightly superior to the 15 units of protamine insulin in intensity of effect, as judged by the consumption of glucose in the hourly periods. Furthermore this effect was continuous, since the active period of 15 to 24 hours for a single dose of 100 units of regular insulin (as shown in the previous paper) must entail a large overlapping of these 12-hourly injections. Nevertheless rat 13 retained appetite for almost the entire time, and the intoxication and death which follow sufficiently large single doses of either regular or protamine insulin remained absent. Furthermore the hypoglycemic tendency ceased within 24 hours after the last insulin injection; in other words there was little or no cumulative effect as compared with a single dose of 100 units, and nothing like the duration of 48 hours or more which is demonstrable for single doses of 250 or 300 units of regular insulin.

#### IV. PROTAMINE INSULIN WITH PARENTERAL GLUCOSE ADMINISTRATION IN CATS AND RABBITS

The uniform fatalities after doses of 150 or 200 units in table 3 seem explainable at least in some instances entirely by the amount of injected glucose. A direct toxic action of the insulinate is evident in some instances; nevertheless with 1000 units the survival was not shortened beyond the limits of accidental variation. The deaths occurred without hypoglycemia, and too early to afford any information as to the possible duration of effects of the subcutaneous injections. The interval before the first convulsive reaction was not greatly different from after regular insulin. The usual hy-dremia, attributed to the glucose injections, was present.

The three intravenous experiments were chaotic. Without preliminary fasting, and with the same dose of 200 units one rabbit died of unknown cause within three hours. The second showed merely nervous symptoms, without acute attacks, for 20 hours. Then a repetition of the dose gave a typical effect in the form of a shortened interval before reaction ( $1\frac{3}{4}$  hours), weakness, hydremia and death. Since it is certain that 200 units of regular insulin under the same conditions will not cause hypoglycemia lasting 34 hours, this experiment confirms the greater duration of the effects of protamine insulin as compared with regular insulin intravenously.

TABLE III  
Cats and Rabbits—Protamine Insulin with Parenteral Glucose Administration

Animals	Weight kg.	Protamine insulin units	Hrs. before 1st reaction	Total glucose required gm.	Total hrs. of treatment	Initial erythrocyte count. Millions	Final erythrocyte count. Millions	Final blood sugar mg.	Result
Cat 1	3.7	Subcutaneously 200	5 $\frac{1}{2}$	58	30	—	—	150	Prolonged prostration. Death.
Cat 2	3.0	1000	—	42	26	7.8	12.5	187	Prostration. Rectal temperature 32° C. Blood concentration due to 20% glucose solution.
Rabbit 1	2.2	10	4 $\frac{1}{2}$	2	7	—	—	—	Easy recovery.
" 2	3.0	20	4	1	4	—	—	—	Easy recovery.
" 3	2.6	50	10	4	14	—	—	240	Death in convulsions, with hyperglycemia.
" 4	3.0	50	5 $\frac{1}{2}$	26	24 $\frac{1}{2}$	—	—	68	Death in convulsions.
" 5	2.0	150	3	37	36	—	—	290	Progressive weakness. Convulsions with hyperglycemia. Death.
" 6	3.1	180	3 $\frac{1}{2}$	10	17	—	—	156	Easy recovery.
" 7	2.0	200	2 $\frac{1}{2}$	17	22	—	—	65	Progressive weakness. Death.
" 8	1.8	200	2 $\frac{1}{2}$	23	21	7.8	3.4	110	Progressive weakness. Death.
" 9	2.2	200	3	26	31	8.4	3.0	290	Progressive weakness. Death.
" 10	2.0	Intravenously 200	—	20	5	7.5	6.4	230	Rapidly progressive weakness. Death.
" 11	2.5	200	—	0	—	—	—	—	Depressed or excited at times, never in danger. Blood sugar ranged 84–113, untreated for 20 hours.
" 11 20 Hrs. later		200	1 $\frac{1}{4}$	20	34	6.8	2.7	89	Weakness. Death in 11 hrs. after last glucose injection; blood sugar in this period 102–89 mg.

A further illustration of this difference with a smaller insulin dose (50 units) is shown in figure 2. A greater intensity of action of the regular insulin was shown by the much earlier onset of hypoglycemic attacks demanding glucose injections, and by the larger quantity of glucose thus required within the first 34 hours; but after that only the protamine animal needed glucose, and this need continued nine hours longer than in the rabbit which received regular insulin.

Fatalities, such as shown in table 3 and also others not tabulated, were escaped in only one instance, again illustrating the variability of individual rabbits. Following a dose of 200 units of protamine insulin subcutaneously on the side of the body (table 4), the most critical period was on the second

day, when there were 12 convulsive attacks. By continuous watching, it was possible to relieve each attack by a prompt subcutaneous injection of 20 c.c. of 10 per cent glucose (in saline) solution. This record is among those which prove that even a long series of violent convulsions, if each at-

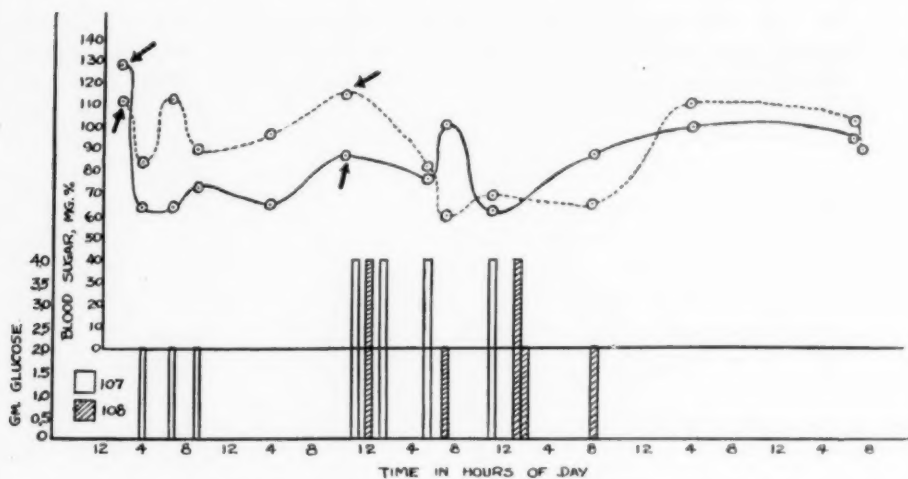


FIG. 2. Rabbit 107 (shown by continuous line) 200 units ordinary insulin, and rabbit 108 (shown by broken line) 200 units protamine insulin, intravenously, on two days. Arrows indicate time of injection.

TABLE IV

One Subcutaneous Injection of Protamine Insulin; Fasting Throughout

Day of Experiment	Rabbit 23—200 Units		Rabbit 24—100 Units	
	Number of Convulsions	Glucose in 10% solution subcutaneously, gm.	Number of Convulsions	Glucose in 10% solution subcutaneously, gm.
1	5	10	11	14
2	12	24	12	15
3	5	10	3	3
4	8	16	3	3
5	10	20	2	2
6	8	16		
7	4	8		
8	2	4		
Total 8 days	54	108 gm.	Total 5 days, 31	37

tack is treated promptly, is not necessarily dangerous or seriously harmful. Numerous blood sugar analyses demonstrated the usual hypoglycemia in the attacks, hyperglycemia following the glucose injections, and considerable intervals of about 80 to 100 mg. per cent between. At the end, a period of

12 hours without convulsions was accepted as evidence that the effect of the insulin was ended. During the long fasting experiment, there were times when the rabbit was apparently willing to eat a little, but most of the time food was refused. At the end it was thin, weak and slightly hungry. Food was taken, first in small and then in large quantities, and full health and strength were rapidly regained. This period of eight full days represents a longer duration of effect of a single dose than has heretofore been reported.

TABLE V  
Food and Glucose Administration after Single Protamine Insulin Injections in Rabbits

Rabbit no.	Insulin Subcut. Units	Food by Stomach	Glucose Subcut. gm.	Duration of Treatment. Hours	Final Blood Sugar mg. %	Result
1	200	400 c.c. 10% glucose by tube.	16	20	180	Progressive weakness. Death.
2	250	20 gm. bread voluntarily. 280 c.c. milk by tube.	2	18	192	No diarrhea or distention. Convulsions. Death.
3	250	450 c.c. milk and 5 gm. glucose by tube.	11	14	85	Slight diarrhea. Death with pneumonia.
4	250	300 c.c. 10% glucose by tube.	23	38	140	Progressive weakness. Death with pneumonia.
5	250	In first 24 hours, refused oats and bread; ate 220 gm. lettuce; given 50 c.c. milk and 100 c.c. 10% glucose by tube; slight diarrhea. Thereafter fasting.	59	104	45	Death probably from prolonged quiet hypoglycemia.

Rabbit 24 in table 4 illustrated a five-day effect of a single dose of 100 units of protamine insulin, given subcutaneously in the lower part of a hind leg. The blood sugar at death was 46 mg. Instead of convulsions, the hypoglycemia in this animal caused mostly a prolonged weakness. This was probably the cause of death, and the animal might perhaps have been saved by the use of larger quantities of glucose on the last three days. The site of injection of a large dose of insulin (body or leg) seems unimportant.

#### V. EXPERIMENTS WITH FEEDING

The failure of appetite after large doses of protamine insulin is still more marked than that observed after regular insulin. Even when a rabbit occasionally acts as if ravenously hungry, proffered food is eaten in only trivial quantity. In the hope of enabling rabbits to tolerate larger insulin doses, attempts were made to increase the intake by offering a variety of foods for voluntary eating and by tube feeding of milk or glucose, with the particular object of reducing the amount of glucose required subcutaneously. As shown in table 5, these attempts with protamine insulin were not as successful as those with ordinary insulin in the preceding paper.

All the rabbits died, though the result in rabbit 5 was apparently due to insufficient glucose. Later experiments have shown that this method can be developed so as to furnish more examples of the true maximum duration of effect of a single dose, such as was illustrated in table 4.

#### VI. REPEATED SUBCUTANEOUS INJECTIONS OF REGULAR INSULIN

In addition to the examples in table 2, tables 6 and 7 show experiments with repeated injections of regular insulin, designed to ascertain to what extent the effects of protamine insulin can be thus imitated.

In table 6, the cat which received five injections of 50 units of regular

TABLE VI  
Cats and Rabbits—Repeated Injections of Regular Insulin Subcutaneously

Animal	Weight kg.	Insulin Dosage	Hours before 1st reaction	Carbohydrate			Total hours of glucose treatment	Final blood sugar mg. %	Result
				Fed gm.	Injected gm.	Total gm.			
Cat	2.2	5×50 units, at 5 hr. intervals	—		32		40	90	Severe prostration. Recovery.
Rabbit 1	2.0	1×50 units; starch and glucose by stomach tube; glucose subcut.	—	9.2	0	9.2	13	108	Slight weakness. Recovery.
Rabbit 1		1×50 units, 24 hrs. later	—	12	40	52	13	122	Apparently well for 13 hours; died during night when unwatched.
Rabbit 2	2.0	2×50 units, at 16 hr. intervals	2½		20		27	80	Progressive weakness; death. Initial erythrocytes 7.7, final 9.8 millions.

TABLE VII  
Rats—Repeated Injections of Regular Insulin Subcutaneously

Rat No.	Weight gm.	Insulin Dosage	Glucose injected Subcut.—gm.				Balance	Total	Total hr. of glucose treatment	Result
			In 1st 6 hrs.	In 2nd 6 hrs.	In 2nd 12 hrs.	In 3rd 12 hrs.				
1	150	3×20 units, 12 hr. intervals	0.8	0.7	1.1	1.7	3.0	7.3	54	Lived.
2	100	2×30 units, 16 hr. intervals	0.3	0.9	1.7	0.6	—	3.5	26	Death, probably from hypoglycemia.
3	195	4×5 units, 6 hr. intervals	0	0.5	1.0	2.8	—	4.3	33	Lived: weak and without appetite for several days.
4	180	8×1 unit, 2 hr. intervals	0.5	1.1	1.0	—	—	2.6	18	Died dyspneic, unconscious: blood sugar 80 mg.
5	190	7×½ unit, 2 hr. intervals	0.8	1.0	0.9	—	—	2.7	23	Death, probably from hypoglycemia.
6	160	12×¼ unit, 1 hr. intervals	0.6	1.5	1.1	—	—	3.2	15	Weakness. Death.

insulin at five-hour intervals became prostrated and required treatment for hypoglycemia for 40 hours. A continuous and sustained effect is neces-

sarily produced by the overlapping of these doses. Differences in the glucose requirement are probably accidental, and the prominent points of distinction seem to be two: (a) the total duration of effect of the multiple doses of regular insulin was much shorter than would undoubtedly be found with a single dose of 250 units of protamine insulin, if the animal could survive; (b) the full toxicity of a single large dose of either regular or protamine insulin was lacking, so that the animal was able to survive.

Rabbit 1 shows that a 50-unit dose, repeated after 24 hours, is more potent the second time than the first time, in respect to the total amount of glucose required for controlling the increased number of hypoglycemic attacks, and also in respect to duration. Death was evidently due to delayed hypoglycemia, after the mistake of stopping the treatment at 13 hours, in imitation of the first day.

Rabbit 2 illustrates a seemingly toxic effect of two 50 unit doses at an interval of 16 hours. The fatality seemed to be not accounted for by hypoglycemia, excessive glucose injections or excessive change in blood concentration. It was noticed in the previous paper that single doses above 100 units can be tolerated by rabbits.

Aside from the cumulative action of the insulin itself, certain harmful legacies from the early doses must be considered. The combination of insulin and glucose perhaps leaves an impoverishment in glycogen. A remaining hydremia due to glucose is illustrated by certain rabbits in table 4 of the preceding paper. It has not been possible, however, to arrive at any clear idea of the conditions under which multiple insulin doses are tolerated sometimes better and sometimes worse than single doses. Factors of both time and total amount are evidently concerned.

In table 7, the first three rats represent survival or merely accidental death with fractionated insulin doses. In each case the aggregate amount is far below what a rat can tolerate in the form of a single injection. The subdivision of this amount results in a marked prolongation of the effect and a correspondingly greater glucose consumption than with a single dose.

Rats 4, 5 and 6 show a tremendously greater efficiency of insulin, as measured by glucose consumption, when the doses are further subdivided into fractions as low as  $\frac{1}{4}$  unit. These results are suggestive in two ways.

First, it seems probable that if the dose of 10 or 15 units were divided into sufficiently small fractions and these injected hour by hour during several days, the full effect of this quantity of protamine insulin might be reproduced with regular insulin. This would confirm the idea that protamine insulin owes its special effect merely to the fact that a large portion of the dose remains for a long time unabsorbed, and the marked physiological action during this time results only from tiny fractions of the dose which enter into metabolism from hour to hour.

Second, another inference may be that the enormous doses of several hundred units are practically without physiological significance, except for furnishing a surplus insulin supply which may remain in the body as long as

several days. With these huge injections also, the effect may be due only to very small amounts which actually enter into metabolism from hour to hour, while the greater part may be destroyed merely as waste material. Clinicians have long known that insulin becomes more efficient unit for unit as it is divided into an increased number of doses. As already mentioned, the exaggeration of these conditions in laboratory animals facilitates study.

It is possible that either continuous intravenous infusion of insulin, or very frequently repeated fractionated subcutaneous doses, as already used by several authors (cf. Bischoff and Jemtegaard,<sup>7</sup> 1937), may be the only accurate method of studying the effects. As already mentioned, however, attention must be given to two points: (a) The very large insulin doses appear to have a specific toxic action, not found with smaller doses, even though the latter may seem to entail an equal glucose consumption. (b) It is difficult to see how very large doses can be studied by the intravenous or fractionated subcutaneous method, without the accumulation of a surplus in the tissues practically on a par with the single massive doses.

#### VII. GLYCOGEN DEPOSITS

Unfortunately, only a few glycogen analyses could be performed by Mr. J. H. Rice. One of the rats represented in table 1, which died after 50 hours of glucose injections following a dose of 10 units of protamine insulin, was found to have 2.1 per cent of glycogen in the liver. Rabbit 5 in table 3, which died after repetition of 200 units of protamine insulin intravenously on the second day, having received 20 gm. of injected glucose in 34 hours, showed 3.1 per cent of glycogen in the liver, 0.9 per cent in the heart and 0.72 per cent in the leg muscles. Three other animals gave positive qualitative tests for liver glycogen.

All the results obtained can be harmonized under one general rule; namely, that animals dying from huge doses of regular insulin are nearly or completely glycogen-free; the controls after glucose alone contain glycogen; and those dying after small subcutaneous or larger intravenous injections of protamine insulin, when there has been heavy glucose dosage with a relatively small insulin influence, have contained more or less glycogen. It must be emphasized that the observations are too few to establish any such broad conclusion, and the supposed rule may be based only on accidents and may be disproved by adequate trial.

#### VIII. CRYSTALLINE ZINC INSULIN

It seemed necessary to consider the possibility of some chemical basis for the peculiarities of protamine insulin, apart from the mere slowness of absorption. Therefore tests were made with insulin crystallized with zinc, as introduced by Sahyun in the laboratory of Frederick Stearns & Co. The great majority of clinical reports (cf. Barach<sup>8</sup>; Sprague and Rynearson<sup>4</sup>; Wilder and Wilbur<sup>6</sup>; and others up to 1937, also a series of papers<sup>10</sup> in

1938) agree that its duration of effect is much less than that of protamine insulin but distinctly greater than that of the ordinary commercial preparations of insulin, and this also has been the writer's experience with patients.

This difference can be clearly confirmed by taking advantage of the exaggerated conditions offered by tests in rats. In table 8, the effects

TABLE VIII  
Rats—Subcutaneous Injections of Stearns Crystalline Zinc Insulin

Insulin Units	Weight gm.	Glucose Injected Subcutaneously				Total Hours of Glucose Treatment	Result
		First 12 hours gm.	2nd 12 hours gm.	Re-maining Period gm.	Total gm.		
20	115	1.5	0.5	—	2.0	16	Prolonged hypoglycemia after last injection. Lived.
40	125	2.5	1.5	—	4.	24	Lived.
60	115	2.5	2.5	1.5	6.5	34	Weakness; death.
100	200	5.	3.5	—	8.5	36	Died 54 hours after last glucose injection.

of 20 and 40 units were decidedly longer lasting than with the same doses of ordinary (Lilly amorphous) insulin in the previous paper, and the apparent glucose equivalent per unit was correspondingly increased. The effects, however, were far shorter than those following protamine insulin; hence fasting rats readily survived after 20 to 40 units of the crystalline insulin, although they died with as little as 10 units of protamine insulin.

In subsequent experiments it has proved possible for rats to withstand 120 units or sometimes more of zinc crystalline insulin (Stearns) without hypoglycemic death, but such animals often lack appetite and die within one to three days later. These late deaths appear to be classifiable among the toxic effects of insulin. This question will be considered further in a subsequent paper, but according to the present evidence crystalline insulin is distinguished from amorphous insulin by toxicity as well as by duration of action. This greater toxicity is probably only a consequence of the more prolonged action. Accordingly, the toxicity as well as the duration of action of crystalline insulin is far less than that of protamine insulin.

#### IX. STORAGE SITE OF INJECTED INSULIN

There is a general belief that the absorption of insulin can be hastened and thus its effect accelerated by enlarging the area of absorption. The present work has not revealed such differences when the differences in injection have been slight. On the other hand, when the effects of large doses injected in one spot are compared with those following injections distributed over 10 or 15 areas, it has been shown that in the latter instance the

effects have been decidedly intensified and shortened. It is of interest that the shortening is more marked than the intensification, so that the glucose equivalent of each unit of insulin is diminished by wide distribution of the dose (thus approaching nearer to the intravenous results).

Other experiments were performed with injections of protamine insulin in the legs as near to the ankle as possible, followed by amputation above the knee. Table 9 shows that the effects can thus be cut short decisively. Life

TABLE IX  
Protamine Insulin Injections in Legs—Amputation

Animal No.	Weight	Prota- mine Insulin Dosage. Units	Hours of Treatment		Glucose In- jected, gm.		Result
			Before Ampu- tation	After Ampu- tation	Before Ampu- tation	After Ampu- tation	
Rat 1	150 gm.	20	36	27	8.8	0.4	Weakness probably due to glucose. Death.
" 2	130 "	20	17	17	3.5	1.0	Weakness ; death.
" 3	220 "	15	9	12	1.6	0.8	Lived.
" 4	120 "	20	12	3	2.5	0.8	Lived.
" 5	225 "	60	20	—	3.8	0	Lived.
" 6	170 "	100	62	—	6.5	2.0	Also drank considerable glucose before amputation. Lived.
Rabbit 1	2 kg.	200	9.	12.	15.	8.	Weakness and death without hypoglycemia.
" 2	2 kg.	200	12	—	8.	1.	Lived. Lively.

is thus saved even after hopelessly fatal doses—up to 100 units of protamine insulin in rats or 200 units in rabbits; also after very long periods, up to a maximum of 62 hours from the time of injection in rats. Generally the injection of a little glucose has been necessary for a short time after amputation, because of either convulsions, weakness, or hypoglycemia as revealed by analyses. In the large strong rat 5, survival was obtained without any glucose after amputation, though the protamine insulin was in the large dose of 60 units and the operation was 20 hours after the injection.

Inspection of the injected area in rats after 20 hours or more showed entire absence of edema or inflammatory signs and strictly normal naked-eye appearances. The complete absorption of the injected fluid seemed obvious. cursory examination of stained microscopic sections has also thrown no light upon the location or state of the retained insulin.

It will be noticed that these results were directly opposite to those described with regular insulin in the preceding paper. Because of the smaller volume of the injection, and the longer time, the absorption of visible fluid was much more complete in the case of the protamine insulin; nevertheless the biologically demonstrable local retention of insulin continued much longer.

The extracellular retention of a combined form of insulin for 62 hours or possibly for still longer periods (e.g. the effects for eight days in the rabbit in table 4) may suggest still greater care in theorizing concerning the limits of the time during which the organism can retain residues of insulin in unknown combinations intracellularly.

There is also an apparent dilemma, as follows: (a) It may be assumed that the greatly prolonged effect (three to five days for 10 to 20 units in rats, eight days for 200 units in rabbits) may be due to a slower absorption than in man. In this case protamine insulin seems to stand alone among all known drugs. (b) It may on the other hand be assumed that the absorption is equally slow in man; i.e., that residues from all protamine insulin doses are still being absorbed five to eight days after injection, and the small animals merely serve as a more delicate indicator because of their sensitiveness to traces of insulin too small for perceptible effects in man. It is necessary to reconcile this assumption with the high tolerance of the animals (especially with spontaneous eating) for regular insulin. Some simple solution would presumably have been arrived at if the experimental program could have been completed. The second assumption seems more probable, especially in view of the results in table 7; and if it be correct that residues from small or large injections are still being absorbed after five to eight days, the cumulative action of protamine insulin receives even a more ample explanation than could have been anticipated from the clinical findings.

#### CONCLUSIONS

1. The tolerance of rats for protamine zinc insulin with spontaneous eating is much lower than for regular insulin, i.e., below 60 units. The loss of appetite, and also the death of rats, rabbits and cats with high doses, seem to show a greater toxicity of protamine than of regular insulin.
2. Under fasting with parenteral glucose injections, the tolerance of average cats and 2-kg. rabbits is below 200 and perhaps below 150 units of protamine insulin. The tolerance of average rats is below 15 units; exceptionally large rats may tolerate 20 units or perhaps more.
3. The duration of the hypoglycemic effect of protamine insulin in animals is greater than has ever been reported before, namely up to five days in rats and eight days in rabbits.
4. This prolonged action of protamine insulin cannot be imitated satisfactorily with repeated large injections of regular insulin, without running into doses enormously higher than the protamine insulin dose. Comparative calculations of the glucose equivalents are thus made irrational. The closest imitation is afforded by doses of only a fraction of a unit of regular insulin repeated at very short intervals.
5. Though small doses of protamine insulin elicit nearly the same rate of glucose consumption as huge doses of regular insulin, they apparently do not have the same "toxic" action. Also a few analyses suggest that they do not have the same effect in depleting glycogen.

6. Comparison with crystalline zinc insulin, which is intermediate in rate of absorption between regular and protamine insulin, gives intermediate results in influence upon glucose consumption and also as to toxicity.

7. Amputation experiments prove that the delayed action of subcutaneously injected protamine insulin is due to retention at the site of injection, for periods tested up to 62 hours.

8. The findings in animals are similar to those in man, but exaggerated in degree. They necessitate the conclusion either that the absorption rate differs in different species, or that active residues of protamine insulin remain in the body for longer periods after injection than heretofore supposed.

9. Since the writer's first publication in 1913,<sup>9</sup> there has been no opportunity of investigating the diuretic action of glucose. The hypothesis of colloid-combined blood sugar in the normal, and free sugar in the diabetic, seems to have been disproved by direct physicochemical tests. It is also evident that the writer's intravenous glucose injections, likewise the subsequent ones of Woodyatt and others, were diuretic only by reason of the injected fluid and of fluid withdrawn osmotically from the tissues, the diuretic agent being the water or saline and not the glucose. In general, hyperglycemia in the normal organism is accompanied not by polyuria but by hydremia, unless the latter is prevented by excessively concentrated solutions. In mild diabetes the urine volume is variable. In severe uncomplicated diabetes, polyuria with heavy glycosuria is the rule; hydremia is unknown and the extreme diuresis may even concentrate the blood. This contrast still seems to represent a fundamental unexplained phenomenon of diabetes, which subsequent investigators have missed even after it had been plainly pointed out. Whether there is this supposed significance or not, and whether the large insulin doses modify this effect of glucose or not, could not be decided under the conditions of the present work; but these observations confirm the actual facts described in 1913, even to the extent of far more extreme hydremia than was then claimed.

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## CASE REPORTS

### ANGINA PECTORIS AS A PREDOMINATING SYMPTOM IN SPONTANEOUS HYPOGLYCEMIA \*

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WHILE the general symptomatology of hyperinsulinism has been known since Harris<sup>1</sup> first recognized the syndrome in 1924, symptoms referable to the gastrointestinal tract, and vague generalized symptoms of varying degrees of severity as are usually observed in the psychoneuroses and in vasomotor disturbances have been the main features described.

We wish to report two cases which have come under our observation in which the predominating symptom was angina pectoris.

#### CASE REPORTS

*Case 1.* A male, 42 years of age, gave a two year history of attacks of substernal pains radiating to both shoulders, coming on with exertion or excitement and requiring complete rest for relief, lasting a variable time (2 or 3 to 10 minutes) and always occurring before meals. There was usually an associated empty feeling in the head, cold sweat and pallor. He was a heavy smoker and had had a chronic cough for many years. Physical examination showed an increase in the aortic width, slight increase in the total cardiac diameter and a rough aortic systolic murmur. The liver was not enlarged; there was no edema. The dorsalis pedis pulses were palpable. The blood pressure was 130 mm. mercury systolic over 95 mm. diastolic. Roentgen-ray examination of the gastrointestinal tract was negative. The basal metabolic rate was normal. The electrocardiographic tracings showed minimal changes (figure 1). The blood sugar tolerance curve showed 59 mg. (fasting), 118 mg. (1 hour); 94 mg. (2 hour); 72 mg. (3 hour); 54 mg. (4 hour). Between the third and fourth hours of the test, the patient complained of marked discomfort and substernal distress, there was a marked pallor and a cold sweat. After the last specimen of blood was taken, the administration of glucose brought prompt relief.

*Case 2.* Male, 39 years of age, with a one year history of attacks of precordial pains, variable in character and lasting a few minutes, radiating to the left shoulder and arm, coming on with exertion or excitement only when he was hungry, rarely when at rest, but then also when hungry. He was a heavy smoker and had had a chronic cough for many years. Physical examination revealed slight sclerotic changes of the retinal vessels; slight increase in the aortic width; the heart was not enlarged; the liver was not palpable; there was no edema; the dorsalis pedis pulses were palpable. The blood pressure was 140 mm. mercury systolic over 90 mm. diastolic. The urine examination was negative. Roentgen-ray examination of the gastrointestinal tract was negative. The basal metabolic rate was normal. The electrocardiographic tracings showed minimal changes (figure 2). The blood sugar tolerance curve was 64 mg. (fasting); 115 mg. (1 hour); 80 mg. (2 hour); 58 mg. (3 hour); 42 mg. (3 hour

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FIG. 1. Electrocardiograms of Case 1.

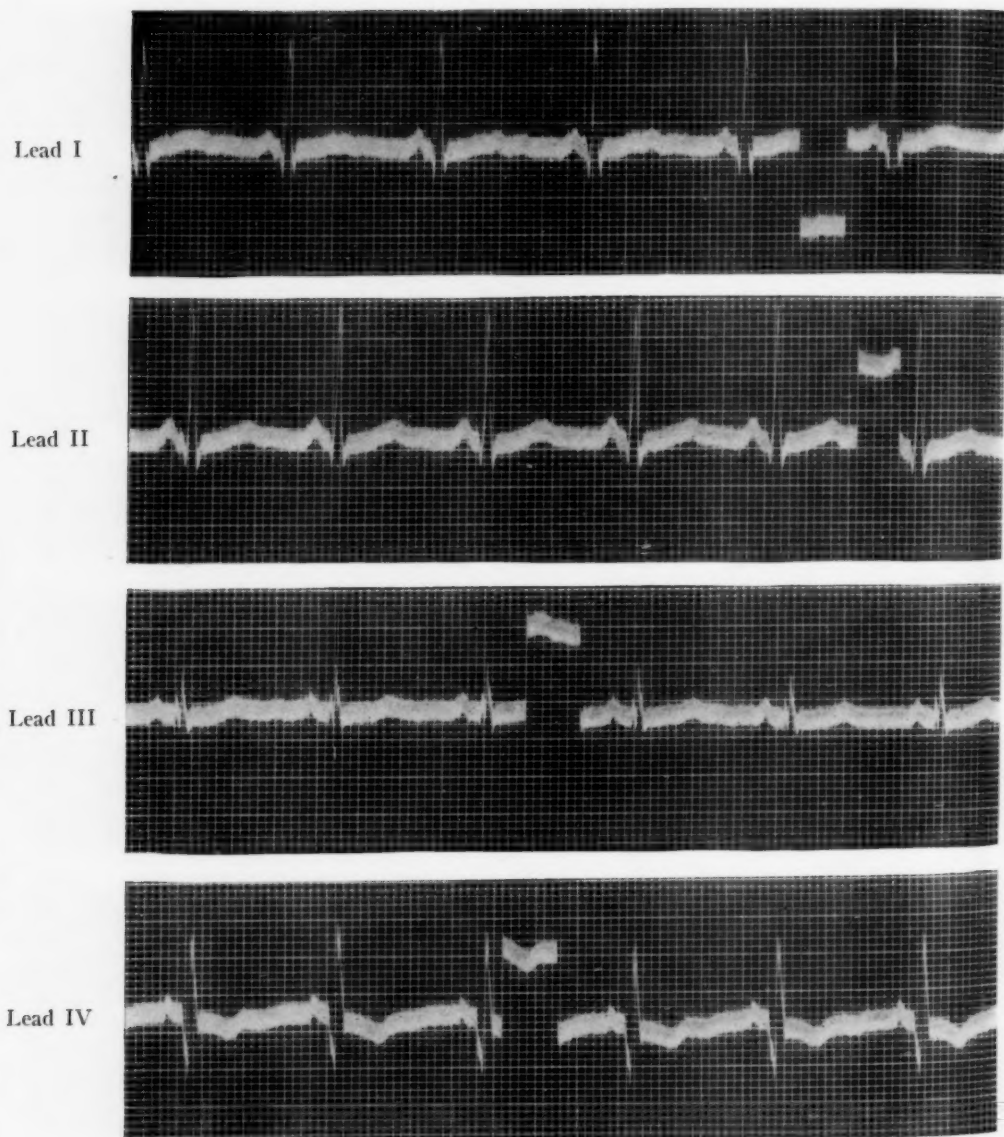


FIG. 2. Electrocardiograms of Case 2.

and 45 minutes). An excruciating attack of precordial pain necessitated terminating the test 15 minutes ahead of time and again the administration of glucose afforded prompt relief.

### DISCUSSION

Harris<sup>1, 2, 3, 4</sup> considered the clinical type of hypoglycemia to be due to excessive insulin secretion by the islands of Langerhans of the pancreas and developed the conception of hyperinsulinism as a disease entity as definite as the opposite condition of hypoinsulinism or diabetes mellitus.

While cases of pancreatic hyperinsulinism have been reported in which on exploration islet-cell tumors have been found (Graham and Womack,<sup>5</sup> Wilder, Allen, and Power<sup>6</sup>), in the majority of cases, the pancreas appears to be apparently normal and these cases must be grouped with diabetes and other functional disorders of the endocrine system.<sup>7</sup> Various etiologic factors have been suggested such as an inheritable constitutional predisposition, low grade pancreatic infection in association with duodenal ulcer, cholecystitis and cholelithiasis (Harris), and various precipitating factors such as excessive ingestion of carbohydrates, infection, trauma, fatigue, exhaustion, and nervous and emotional disturbances. There may be an association of hyperinsulinism with other endocrine lesions such as adrenal or pituitary tumor or hyperthyroidism.

Harris, in discussing the symptomatology, considered several types. The mild type where the attack consists of weakness, anxiety, pallor, especially about the lips, sweating and trembling occurring with hunger and relieved by the ingestion of sugar. The moderately severe type where there is profuse sweating, palpitation, prostration, more marked anxiety, mental lapses, periods of unconsciousness, and spasms of isolated groups of muscles (attacks resembling petit mal) also occurring with hunger and relieved by ingestion of sugar. The severe type where there are recurring attacks of unconsciousness, convulsions, narcolepsy, associated perhaps with major hysteria or actual psychosis (attacks may resemble grand mal epileptic seizures). The type where abdominal pain is the main feature, often suggesting an acute surgical abdomen, here again attacks occurring with hunger and relieved with the ingestion of sugar.

In our cases, while there were features of the other types, the predominating symptom and the one for which they sought medical aid was angina pectoris. In both of our cases, the relationship of the angina to hunger was brought out only on direct questioning and in both the relief of the attack with the ingestion of sugar was prompt.

The characteristic blood sugar tolerance curve shows unusually low readings throughout or a normal peak with subsequent depression of figures far below that observed in normal cases. Harris brought out that "one fasting blood sugar determination or one glucose tolerance test is not always sufficient because there seem to be periods when the patient with hyperinsulinism will show normal readings. The element of mental and physical fatigue affects both blood sugar levels and in making the tests the patient should not be permitted to lie down. In some cases, the blood sugar levels may remain normal for the first four hours and fall to very low levels in the fifth and sixth hours."

While ingestion of sugar will control the immediate attack, it also stimulates insulin production, so that a large dose of sugar may provoke a more severe attack several hours later. Harris and others have advocated a low carbohydrate,

moderate protein and high fat diet, providing approximately 1 to 2 gm. carbohydrate, 1 gm. protein and 2 to 2.5 gm. fat per kilo of body weight per day divided into six to eight portions. More carbohydrates must be given in the more severe types. Frequent blood sugar determinations should be made in the regulation of the diet.

Both of our cases presented strikingly similar features. The patients were males, around 40 years of age, short, stocky with a tendency to obesity. They were heavy smokers and though the changes on the electrocardiograph tracings were negligible, they had some evidence of early sclerotic vascular changes. The blood sugar tolerance curves were characteristic in both cases showing a low fasting sugar, a peak below the average normal and a rapid drop to subnormal figures. The pains, in both cases, were substernal or precordial in type and while they occurred with exertion or excitement, there was a definite relationship to hunger and the ingestion of glucose brought prompt relief. Both cases were treated with diets similar to those discussed above and have remained free from attacks.

#### SUMMARY AND CONCLUSIONS

The subject of spontaneous hypoglycemia is briefly discussed and two cases in which angina pectoris was the predominating symptom are reported. The similarity of the clinical picture, the characteristic sugar tolerance curves and the prompt response to dietary measures are discussed. The importance of inquiring into the association of anginal pains with hunger, even though the attacks are also definitely related to effort or excitement, is stressed.

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## OCCLUSIVE ARTERIAL DISEASE OF THE LOWER EXTREMITIES ASSOCIATED WITH LIPEMIA AND XANTHOMA TUBEROSUM\*

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IN the past two years two patients have been observed at the clinic who presented the clinical picture of occlusive arterial disease of the legs, xanthoma tuberosum of the skin and marked lipemia.

The first patient was a man, aged 46 years, of Welsh and French ancestry, who apparently always had enjoyed good health. He complained solely of typical intermittent claudication of the calves of both legs of seven years' duration which had become progressively more severe. He smoked an average of 25 to 30 cigarettes a day; he gave no history of phlebitis, pain or trophic changes in the toes, or any symptoms referable to the upper extremities. Nodular yellow cutaneous lesions in the region of the elbows and of the knees had been present for 12 years and scattered, small, yellowish papulo-squamous lesions of the trunk had been present for six years. His past history and family history were negative.

The nodular cutaneous lesions were typical of xanthoma tuberosum. Pulsations were absent in the popliteal, posterior tibial and dorsalis pedis arteries of both legs, were slightly diminished in the left femoral artery and were normal in the right femoral, and both brachial, radial and ulnar arteries. There was definite pallor of both feet on elevation of them and slight reactionary rubor of the toes on dependency. The patient was of normal build and weight. General physical examination otherwise gave negative results. No abnormalities were seen in the ocular fundi. Blood pressure, urine, concentration of hemoglobin and number of erythrocytes and of leukocytes were normal; roentgenographic examination of the thorax and Kline test of the blood gave negative results. The electrocardiogram was negative. Roentgenographic examination of the thighs and legs revealed no evidence of calcification of the arteries. A glucose tolerance test gave normal results, the maximal value for blood sugar being 146 mg. per 100 c.c. and no glycosuria being induced. The value for blood cholesterol was 667 mg. per cent, that for fatty acids was 1554 mg. and that for total lipoids was 2221 mg.† Intermittent claudication was produced in the calves of both legs by employment of a standard test in which the patient walked at the rate of 120 steps per minute. The symptoms appeared in from 6 minutes and 38 seconds to 7 minutes and 13 seconds on three successive days. This patient was given a diet low in content of fat and cholesterol and was observed at intervals during a period of 21 months. Subsequent determinations of the lipoids of the blood are given in table 1. During the period mentioned, the patient's general health remained good. At the last examination pulsations were unchanged from those observed at the previous examinations; postural changes in color had disappeared and the claudication did not develop until 20 minutes after the walking test was begun.

The second patient was a woman, aged 49 years, of English and Irish ancestry, who presented herself at the clinic and gave a history of numerous symptoms of a number of years' duration: migrainous headaches, fatigability, nervousness, attacks of vertigo, shortness of breath on exertion, palpitation of the heart, gaseous indigestion, intermittent diarrhea and failure of mental concentration. In addition, one com-

\* Read before the meeting of the Central Society for Clinical Research, Chicago, Illinois, November 5, 1937.

† All determinations of the lipoids of the blood mentioned in this report were done on plasma. The determinations of concentration of cholesterol, of fatty acids, and of total lipoids were made by the Bloor method, that of lecithin by the Whitehorn method.

TABLE I  
Values for Blood Lipoids in Milligrams per 100 c.c., Case 1

Date	Total cholesterol	Cholesterol esters	Lecithin	Fatty acids	Total lipoids
9-19-35	667			1554	2221
10-18-35	476			1283	1759
12-14-35	463			1267	1730
2-29-36	463			1003	1466
5-26-36	555		510	1286	1841
8- 5-36	476	320	520	1310	1786
10-11-36	476		478	1389	1865
2- 8-37	340	260	390	935	1275
6- 4-37	407		378	666	1073

plaint was of pain in the calves of both legs induced only by walking and rapidly relieved by standing still. This had been noted for six months. The patient also stated that yellowish, nodular lesions of the skin of the elbows, knees, feet and dorsal surfaces of the hands had been present for 10 years.

The lesions were typical of xanthoma tuberosum. Pulsations were absent in both posterior tibial arteries, were definitely reduced in the right dorsalis pedis artery and were barely palpable in the left dorsalis pedis artery; pulsations were present and normal in the popliteal, femoral, brachial, radial and ulnar arteries. No postural changes of color were noted. General physical examination was otherwise objectively negative. Nothing abnormal was noted in the ocular fundi. Blood pressure, urine, concentration of hemoglobin and number of erythrocytes and of leukocytes were normal; the Kline test of the blood and roentgenographic examinations of the thorax, legs and thighs gave negative results. The concentration of blood sugar (fasting) was 79 mg. per 100 c.c.; the basal metabolic rate was minus 7 and the electrocardiogram was normal. Examination of the blood lipoids gave evidence of marked lipemia; the concentration of cholesterol was 657 mg. per cent, that of fatty acids 1018 mg. and that of total lipoids 1675 mg. Biopsy of one of the nodular cutaneous lesions on the elbow demonstrated a histologic picture typical of xanthoma tuberosum. Intermittent claudication was produced in the calves of both legs by employment of the standard walking test after 2 minutes and 51 seconds. This patient was also given a diet low in content of fat and cholesterol. Subsequent determinations of the lipoids of the blood are given in table 2. During the period of observation symptoms of intermittent claudication and pulsations of the arteries of the legs remained unchanged.

It will be noted that although there was a definite reduction in concentration of lipoids in the blood in both cases during the period of dietary treatment, the concentration of lipoids did not drop to a level within normal limits. The diets contained approximately 30 gm. of animal fat a day. Attempts were made to give these patients diets which contained less than 2 gm. of animal fat a day and very little cholesterol. These diets were tolerated very poorly. In both cases marked fatigability and weakness of muscles developed but these symptoms may

TABLE II  
Values for Blood Lipoids in Milligrams per 100 c.c., Case 2

Date	Total cholesterol	Cholesterol esters	Lecithin	Fatty acids	Total lipoids
4-14-36	657			1018	1675
4-23-36	595			1050	1645
4-29-36	667			766	1433
9- 5-36	333			787	1120
12-24-36	416			666	1082
6-18-37	416	298	402	661	1077
6-30-37	396	278	402	880	1276

have been owing to deficiency of the diet in some factor other than fat and cholesterol. Finally, the diets were discontinued voluntarily by both patients and the diets originally used were resumed.

The association of xanthoma tuberosum of the skin with increased concentration of blood lipoids has been emphasized recently by Montgomery and by Montgomery and Osterberg, who found definitely high values in almost all of the cases they studied. The chief purpose of this paper is to call attention to the possible relationship between the hyperlipemia and hypercholesterolemia on the one hand and the occlusive arterial disease on the other. In the absence of pathologic studies of the blood vessels, the nature of the arterial lesion can only be inferred. The two common chronic occlusive arterial diseases of the legs are thrombo-angiitis obliterans and arteriosclerosis obliterans. Although blood lipoids may be slightly elevated when either of these conditions is present, their concentration does not approach the high levels observed in the two cases herein reported (table 3). The onset of intermittent claudication in the fourth or fifth

TABLE III  
Plasma Lipoids in Occlusive Arterial Disease of the Legs

	Cholesterol		Fatty acids		Total lipoids	
	Range	Average	Range	Average	Range	Average
Normal	160-200	180	200-250	225	500-550	525
Thrombo-angiitis obliterans (Roth and Allen, 36 cases)	102-273	192	194-603	377	360-871	563
Arteriosclerosis obliterans, 12 cases	191-321	278	324-593	432	515-791	691
Case 1, this report	667		1554		2221	
Case 2, this report	657		1018		1675	

decade of life always engenders the suspicion that thrombo-angiitis obliterans is present, but neither of the patients whose cases have been reported had experienced superficial phlebitis or involvement of the arteries of the upper extremities which, when present, are distinguishing characteristics of thrombo-angiitis obliterans; also, thrombo-angiitis occurs very rarely among women. Typical arteriosclerosis obliterans of the legs rarely is seen before the age of fifty, but it does occur. The absence of evidence of calcification of the arteries in the roentgenograms does not preclude the presence of such a lesion. The most likely possibility is that the arterial lesions were premature extensive atheromatous formation accompanied by a minimal degree of degenerative change in the medial coat. It is well known that atheromatous lesions have some of the features of xanthoma tuberosum and usually contain rather large amounts of fat and cholesterol. In 1936, Ochsner and Conner reported a case in which the values for blood lipoids were high (cholesterol 667 mg.; fatty acids 1971 mg.) and the patient died of coronary occlusion at the age of 55 years. Diabetes mellitus and xanthoma tuberosum were not present. Necropsy disclosed extensive atheromatosis of the aorta and of many large arteries; the atheromas contained an abnormally large amount of cholesterol and lipid material.

Association of excessive formation of atheromas in the heart and blood vessels with xanthoma of the skin was noted by Fagge in 1873, and by Lehzen and Knauss in 1889. A peculiar type of atheromatosis, characterized by numerous foam cells, in association with xanthomatosis of the skin and with diabetic coma was reported by Oppenheimer and Fishberg in 1925. Montgomery reported that in more than 25 per cent of his series of cases of xanthoma tuberosum, clinical evidence of coronary sclerosis and angina pectoris was present.

There is certainly reason to believe that association of the hyperlipemia and hypercholesterolemia with occlusive lesions of the arteries as noted in the cases I have described is more than incidental. Ignatowski, in 1908, observed atheromas in the aortas and large arteries of rabbits after they had been fed milk, and egg yolks. Similar lesions were produced by Anitschkow and Chalutow by feeding rabbits pure cholesterol. This work was confirmed by Bailey in 1916 and by Leary in 1934 who have stated that the lesions were identical with those of atheromatosis as observed in human subjects. It is interesting that the xanthomatous lesions of the skin appeared five years before the intermittent claudication in my first case and more than nine years before, in my second case, and it can be assumed that concentration of the blood lipoids was, at least, somewhat increased during these periods.

It would seem that there is sufficient reason to attempt to reduce the lipemia in these cases. As noted, this reduction was obtained partially in both cases by means of the diets low in content of fat. Coincidentally with the reduction in concentration of lipoids of the plasma the symptoms and signs of the vascular disease improved in one instance but remained stationary in the other. There has been no clinical evidence of further vascular occlusion.

Finally, I wish to emphasize Montgomery's statement that peripheral arterial disease may occur in association with xanthoma tuberosum. As this type of xanthomatosis may be asymptomatic, patients who have peripheral arterial disease should be examined carefully for evidence of xanthomatous lesions and patients who have xanthomatous lesions should be examined carefully for evidence of peripheral arterial lesions.

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## EDITORIAL

### *SERUM LIPASE IN THE DIAGNOSIS OF THE DISEASES OF THE PANCREAS*

Until 1932, investigators of diseases of the pancreas used the concentration of that fat-splitting enzyme in the serum which is capable of splitting simple esters (esterase) in the diagnosis of pancreatic disease; but the results were too variable to be of great value. In 1932, Cherry and Crandall<sup>1</sup> re-examined the problem of fat-splitting enzymes in the serum, finding that the activity of the esterase as measured by hydrolysis of ethyl butyrate or tributyrin was affected in one of three ways: it was increased, decreased, or was not changed following experimental ligation of the pancreatic duct of dogs. They therefore concluded that the esterase did not respond according to any definite pattern.

This explained the discordant results obtained by the investigators who had used simple esters as substrates in the study of pancreatic lipase in the blood. In contrast to the variability of the influence of experimental ligation of the pancreatic duct on the values for ester-splitting enzymes in the serum, these authors showed that an enzyme capable of splitting olive oil (lipase) appeared regularly in the blood stream of dogs in large amounts following the same procedure. Hence, the appearance of this enzyme in the blood made possible the development of a promising test for the detection of pancreatic disease.

The degree of lipase activity of the serum was determined by the amount of olive oil hydrolyzed by a given quantity of serum in a given period of time. The value is expressed in terms of cubic centimeters of twentieth-normal sodium hydroxide used to neutralize the fatty acids liberated by 1 c.c. of serum. Cherry and Crandall<sup>1</sup> found that an olive-oil-splitting lipase was absent from the blood of dogs.<sup>1</sup> They also found that the sera of only six of the 146 dispensary patients contained even a trace of olive-oil-splitting enzyme. Comfort and Osterberg, on the contrary, reported that, using the method of Cherry and Crandall, they observed an olive-oil-splitting lipase which was almost constantly present in small amounts in the sera of persons free from abdominal disease who were examined at The Mayo Clinic. Comfort reported that the range for values of lipase in the serum in persons free from abdominal disease was between 0.2 c.c. and 1.5 c.c. twentieth-normal sodium hydroxide per 1 c.c. of serum. The most frequent values were 0.6, 0.7, 0.8, and 0.9 c.c. This discrepancy in normal values undoubt-

<sup>1</sup> CHERRY, I. S., and CRANDALL, L. A., JR.: The specificity of pancreatic lipase: its appearance in the blood after pancreatic injury, *Am. Jr. Physiol.*, 1932, c, 266-273.

<sup>2</sup> COMFORT, M. W., and OSTERBERG, A. E.: Lipase and esterase in the blood serum; their diagnostic value in pancreatic disease, *Jr. Lab. and Clin. Med.*, 1934, xx, 271-278.

<sup>3</sup> COMFORT, M. W.: Serum lipase; its diagnostic value, *Am. Jr. Digest. Dis. and Nutrition*, 1937, iii, 817-821.

edly depends on slight differences in technic and should disappear as the method becomes standardized.

Elevated values for lipase in the serum occur regularly following experimental ligation of the pancreatic duct in dogs<sup>1</sup> and also after experimentally produced pancreatitis.<sup>4</sup> Experimental ligation of the pancreatic duct always has been followed within a few hours by a rapid rise in values for the lipolytic activity in the serum, which returns to normal in about ten days, even though the ligatures are intact and the obstruction is complete. Apparently, the glandular tissues cease to secrete after a certain length of time; but secondary rises in concentration may occur later. Similarly, pancreatitis experimentally produced by the injection of bile into the pancreatic ducts of dogs has been uniformly followed by a rise in values for serum lipase. The concentration returns to normal levels as the inflammation subsides; this usually occurs within seven to ten days after this procedure. The elevation of values following both experimental procedures is presumably the result of reabsorption, although there is evidence tending to indicate that pancreatic enzymes may be secreted into the blood stream.<sup>5, 6, 7</sup> The rapidity of the occurrence of elevated values following these experimental procedures and the definite limitation of the duration of elevation of values will be found especially significant in the interpretation of the behavior of values for lipase in clinical conditions.

Substantial clinical experience with the stimulation of the activity of lipase in the serum as a test of pancreatic disease has also been reported.<sup>2, 3</sup> Values for lipase up to the amount of 10 c.c. of twentieth-normal sodium hydroxide per 100 c.c. of serum have been reported when disease of the pancreas has been present. Values for serum lipase were elevated in 15 of 41 cases (36 per cent) in which malignant disease of the pancreas was demonstrated at operation and in three of five cases of carcinoma of the ampulla of Vater.<sup>2</sup> Such a low percentage of elevated values accompanying malignant disease of the pancreas may be accounted for by the fact that elevated values are found only when the carcinoma has obstructed the pancreatic ducts and when the determinations are carried out during the time that the gland is actively secreting into an obstructed duct. It is clear from these figures that a normal value for serum lipase does not exclude the possibility of malignant disease of the pancreas.

Inflammatory disease of the pancreas, however, presents a much different picture.<sup>3</sup> Elevated readings for serum lipase could be found in 95 per cent

<sup>1</sup> BAXTER, HAMILTON, BAXTER, S. G., and McINTOSH, J. F.: Variations in the level of serum lipase in experimental pancreatitis, *Am. Jr. Digest. Dis. and Nutrition*, 1938, v, 423-425.

<sup>2</sup> ANTROPOL, WILLIAM, SCHIFRIN, ARTHUR, and TUCHMAN, LESTER: Blood amylase response to acetylcholine and its modification by physostigmine and atropine, *Proc. Soc. Exper. Biol. and Med.*, 1934, xxxii, 383-385.

<sup>3</sup> FRIEDMAN, IRVING, and THOMPSON, W. R.: Induced and spontaneous changes in blood amylase particularly in relationship to the pancreas; an experimental study, *Ann. Surg.*, 1936, civ, 388-402.

<sup>4</sup> TUCHMAN, LESTER, SCHIFRIN, ARTHUR, and ANTROPOL, WILLIAM: Blood amylase response to acetyl-beta-methylcholine chloride in pancreatectomized dogs, *Proc. Soc. Exper. Biol. and Med.*, 1935, xxxiii, 142-144.

of cases of subacute or acute pancreatitis, provided the readings were taken during the acute phase of the inflammation or within the first few days of the onset of the disease. Elevated values have been obtained occasionally as late as 21 days after the initial attack, but in these cases there was clinical evidence of exacerbation of the inflammation. The lone exception to the general rule that elevated values occur during the acute phase was found in a case of pancreatic necrosis, the normal value in this instance being attributed to widespread destruction of the architecture of the pancreas and absence of functioning pancreatic tissue. Elevated values will apparently be found with great regularity in subacute or acute pancreatitis, provided the acute process has not subsided and that some functioning pancreatic tissue remains intact. Elevated values have not been encountered after the acute process has subsided or in the presence of chronic atrophic pancreatitis.

Individual determinations of the activity of lipase in the serum appear to furnish an efficient test for acute or subacute pancreatic disease, but they are of considerably less value in testing for the presence of malignant disease of the pancreas. It must be emphasized, however, that elevated values do not distinguish the types of pancreatic disease present in the individual case. This point must be determined by the clinical and physical findings. If values are repeatedly determined and curves are constructed therefrom, the type of curve resulting may prove somewhat distinctive of the type of pathologic condition present. If values for serum lipase rise rapidly following an acute attack of upper abdominal pain and then fall rapidly to normal levels, the physician may safely assume that such behavior favors the presence of pancreatitis. If the values for lipase in the serum in the presence of a painless jaundice are increased and remain at a fairly constant level, carcinoma of the head of the pancreas is probably present.

Elevated values for lipase suggest the presence of pancreatic disease in a great majority of cases. The fact that elevated values do not necessarily imply the presence of pancreatic disease in cases of obstructive jaundice must be considered, however, for it has been shown that experimental ligation of the common bile duct is followed by a marked rise in values for lipase.<sup>8</sup> Moreover, Comfort has reported such elevated values in 19 cases of jaundice, most of which were caused by obstruction of the duct by stone or stricture. While the pancreas was not examined by the surgeon in these 19 cases and while the pancreas cannot be excluded as a cause of the elevated values, the additional possibility that the obstruction of the common bile duct was responsible for the elevations of values in these cases must be thought of. But, on the contrary, Comfort's report that in 26 cases of obstructive jaundice caused by carcinoma of the head of the pancreas, and in 62 cases of jaundice (most of which were obstructive in type and the result of stone or stricture of the common bile duct) normal values were obtained, is strong evidence that obstruction of the duct rarely will be the cause of elevated

<sup>8</sup> CRANDALL, L. A., JR., and CHERRY, I. S.: The regulation of blood lipase and diastase by the liver, *Am. Jr. Physiol.*, 1931, xcvi, 515-516.

values for lipase and so lead to an erroneous diagnosis of pancreatic disease. Since it is possible that these elevations are sometimes the result of obstruction of the common bile duct, elevated values for lipase in cases of obstructive jaundice must be interpreted with this possibility in mind until the chance of error from this source is more fully determined.

It seems safe, therefore, to conclude (1) that elevated values for lipase in the serum point with a high degree of certainty to the presence of benign or malignant disease of the pancreas associated or not associated with acute or chronic disease of the gall-bladder, with cholangitis, with choledocholithiasis or with stricture of the common bile duct, and (2) that while elevations of values for lipase in the serum are probably not specific for the presence of pancreatic disease, the test may be used to advantage in the diagnosis of malignant disease of the pancreas or acute or subacute pancreatitis. Certainly, its diagnostic possibilities are so attractive that further clinical application of the test, carefully controlled by pathologic studies of the pancreas at the operating table, is highly desirable.

M. W. C.

## REVIEWS

*The Spectacle of a Man.* By JOHN COIGNARD, M.D. 252 pages; 21 × 14 cm. Jefferson House, Inc., New York City. 1937. Price, \$2.50.

This book is an attempt by a psychiatrist, under a pseudonym, to show the changes in his patient's social relationships which occurred during a period of psychoanalysis. The book is well written and interesting but it gives evidence of superior novel writing ability and only questionable evidence of a knowledge of psychotherapeutic procedure. In brief, the plot, supposedly based on a real story from the diary of the man who was being analyzed, tells of a shy and stammering engineer who fell in love, developed an affair and then when his analysis was about over, rejected his mistress and found another woman to whom his marriage is implied at the end of the book. The mistress was fortunate, for the patient became very prosy and dull.

The volume starts out well from the standpoint of demonstrating analytic procedure with a letter from the patient and an office interview which includes a good interpretation of a dream. Other psychoanalytical material appears from time to time in the volume which is somewhat entertaining but contains a great deal of philosophizing about the relations of people to each other according to rather naïve but not unsound psychoanalytical tenets. The value of the book as a means of teaching psychoanalysis is dubious—in fact it is even somewhat misleading; but, as a literary contribution it is superior to many "psychoanalytic novels" and the scattered discussions of psychoanalytic technic are interesting and might be revealing to an interested layman. Apparently for purposes of publication, the sexual picture is softened and this tends to vitiate the analytic picture presented.

L. S. S.

*Handbook of Hematology.* In 4 volumes. Edited by HAL DOWNEY, Professor of Anatomy, Medical School, University of Minnesota, Minneapolis. Thirty-seven contributors. 3136 pages. 1448 illustrations, including 50 colored plates. Paul B. Hoeber, Inc. (Medical Book Department of Harper Brothers), New York. 1938. Price, \$85.00 set. Volume one—pages 1-698.

The publication of this Handbook is significant of the great interest with which the study of hematology is being pursued in all centers of medical research in the United States. This work fills a long existent gap in the English and American literature devoted to hematology. It places at the disposal of all interested in this subject an authoritative, scholarly and critical evaluation of the significant data culled from a world literature of tremendous proportions. The subject is approached from the standpoint of its position as a branch of biological science and hence a large proportion of the entire work, fully one-half, is devoted to a consideration of the fundamental scientific aspects of the field. This necessitates a detailed study of the morphological minutiae of the hematopoietic tissue of both the embryonic and adult human body as well as discussion of comparative hematology. There is of necessity some overlapping of those sections dealing only with a single type of blood cell and those concerned with the origin and interrelationships of these cells. The editor has permitted the contributors a considerable degree of freedom and hence there are divergences of opinion. However, one finds here an equitable expression of all important points of view. The results are both stimulating and thought-provoking to the interested reader. The blood dyscrasias are likewise dealt with in a competent and detailed manner by men who have frequently contributed much original work toward the elucidation of their particular topic.

Volume 1 of the Handbook is concerned almost entirely with a consideration of the fundamental data pertaining to the formed elements of the circulating blood. There are eleven sections, some of which are of monographic proportions. These include chapters on the erythrocytes; the polymorphonuclear neutrophile leukocyte; the eosinophile leukocytes and eosinophilia; the mast cells, including both the tissue and mast leukocyte (basophile); the lymphocytes and monocytes; and the blood platelets and megakaryocytes. There are, in addition, sections on the functions of the leukocytes and three chapters detailing the pros and cons of the supravital method of studying blood cells. The only purely clinical section in this volume is that devoted to a consideration of the hemorrhagic diatheses.

It is obviously impossible within the scope of a brief review to examine critically all the controversial theses discussed. In general it can be stated that the material is presented in such a manner and with such careful documentation that the reader is often stimulated to form his own opinions concerning the data. The existence of so many lacunae in our knowledge of hematology frequently gives a tentative air to many of the discussions. In the section on lymphocytes and monocytes there is a detailed exposition by Bloom of the extreme unitarian theory of blood formation. Included in the same chapter, however, are schemata presenting the other important theories of hematopoiesis. The careful experimental and histological data supporting the monophyletic view of blood cell formation go far toward making this an attractive and rational working thesis. With the introduction of bone marrow biopsy as a clinical diagnostic aid this heretofore academic controversy becomes of vital interest to the clinician. The discussion of hemorrhagic diatheses in volume one illustrates one obvious defect in this type of publication, i.e., its immobility. In dealing with the blood defect in jaundice, for example, there is no mention made of the newer work with vitamin K. The classification of hemorrhagic diatheses does not include the interesting though uncommon "constitutional thrombopathy" of von Willebrand.

The format of the book, its profuse illustrations and extensive bibliographies cannot be commended too highly. It will certainly remain for many years the most authoritative source book for all seeking information in this field and should, moreover, provide a stimulus for further progress in hematology.

M. S. S.

*A Historical Chronology of Tuberculosis.* By RICHARD M. BURKE, M.D. 84 pages; 19.5 × 13 cm. Charles C. Thomas, Springfield, Illinois. 1938. Price, \$1.50.

This small but concise book presents the development of our knowledge of tuberculosis. It is arranged in outline form with the passing years as subheadings to indicate progress.

We find that in general, tuberculosis has developed in the same pattern as the whole field of medicine. The ancient period concerned itself largely with description of the disease. The pre-modern developed the knowledge of anatomy, while the modern period witnessed the development of pathology and bacteriology and finally the climax of our knowledge with Koch's discovery of the tubercle bacillus. Then followed the development of therapy, the rise of anti-tuberculosis activities, and we are brought to the present day concepts.

While of minor value, the book is interesting in that it orients the present with the past and enables one to visualize at a glance the progress of knowledge in this particular field.

M. J.

*Biological and Clinical Chemistry.* By MATTHEW STEEL, Ph.D. 770 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1937. Price, \$8.00.

The author has presented a biochemistry textbook in which attention is pointed toward clinical applications. The book combines theoretical discussions with experiments pertinent to them, often repeating the experiments in different parts of the text. The chapters on vitamins and hormones are especially comprehensive and cover the literature to 1936. References are given at the end of each chapter and suggestions made for further and more complete reading. The book will be useful in laying the foundation for further study and experimentation.

E. M. R.

*Fundamentals of Experimental Pharmacology.* By TORALD H. SOLLMAN, M.D., Sc.D., and PAUL J. HANZLIK, A.M., M.D. 307 pages; 23.5 × 16 cm. J. W. Stacey, Inc., San Francisco. 1939. Price, \$4.25.

Ten years have elapsed since the first publication of this book on experimental pharmacology and those concerned with the teaching of this subject to medical students from an experimental view point welcome the revision of this standard text in the field. The second edition continues the original plan of the first by dividing the text into two general parts: first, Chemical Pharmacology, and second, Experimental Pharmacodynamics. The aim of the author is to provide the fundamentals of Pharmacology for medical science, public health, industry, government agencies and train the students for the fulfillment of these responsibilities by means of a rounded out, practical course of exercises using well-tested methods. Among the subjects treated by the book are, pharmaceutical preparations, incompatibilities, toxicology, adsorption of drugs, osmotic and colloidal phenomena, protoplasmic poisons and anthelmintics. Under experimental pharmacodynamics the action of drugs on the various systems of the body are treated under: central nervous system, cardiac muscle, respiratory reactions, circulatory correlations and changes in urine flow.

The appendices to the book are of special interest containing lists of the equipment necessary for the experiment and the extraordinary useful table of the doses of drugs for various animals required to produce definite effects.

The pharmacologist welcomes the revision of this standard book for experimental work in this ever broadening field.

J. C. K., JR.

## COLLEGE NEWS NOTES

### FIFTIETH ANNIVERSARY OF THE JOHNS HOPKINS HOSPITAL

The fiftieth anniversary of the opening of the Johns Hopkins Hospital was the occasion of a three day celebration attended by a large gathering of the alumni of this institution as well as by many distinguished guests. In one of the opening sessions the greetings of the American Medical Association, of the American Nurses Association, of the American Hospital Association, of the American College of Surgeons and of the American College of Physicians were conveyed in brief addresses by their respective Presidents. These were followed by the principal address of the occasion which was delivered by Dr. James B. Herrick, F.A.C.P. The speech of greeting by the President of the College, Dr. O. H. Perry Pepper, follows:

#### GREETINGS TO THE JOHNS HOPKINS HOSPITAL ON THE OCCASION OF ITS FIFTIETH ANNIVERSARY CELEBRATION, MAY 4, 1939

By O. H. PERRY PEPPER, M.D., President of the American College of Physicians

The American College of Physicians is deeply appreciative of the opportunity to join in this well-justified celebration of the Fiftieth Anniversary of the opening of the Johns Hopkins Hospital.

Its founder, Johns Hopkins, was a member of the Society of Friends and in their phraseology believed that he would "be given to see" how to dispose of his wealth. Would that today he might be "given to see" the wonderful results of his wise bequests! For the foundation of the Johns Hopkins Hospital initiated one of those major advances by which medicine progresses; sometimes it is a discovery such as those of Pasteur or Koch, sometimes a new method, sometimes a new vision stimulating others to convert the vision into reality.

From the opening of the new Hospital untrammelled by tradition, there came new life into medicine as a whole and especially into the teaching and science of medicine, for this was the beginning of real clinical teaching in this country and of the merging of student, interne, resident and staff into one coördinated team for the study of patient and disease.

Let others recall for us the whole brilliant roster of the staff and administration from 1889 to the present. As internists, the Fellows of the American College of Physicians derive their special inspiration not only from this hospital's great first Physician-in-Chief—William Osler, but also from his eminent successors—Barker, Janeway, Thayer and Longcope. Five names to conjure with; five individuals but one unbroken stream of influence; a constant spring from which there have flowed scientific advances and an endless group of internists trained in the Hopkins tradition.

Internal medicine owes much to these five Physicians-in-Chief. The field of internal medicine would not be what it is today if Osler's Textbook and Osler's System of Modern Medicine had not been written; if Barker had not clarified the technic of modern diagnosis in his system, Monographic Medicine. Janeway set us a new standard in giving up the rewards of an almost limitless practice to initiate the full-time experiment; Thayer the many-sided, a leader in medicine, in medical science, in the army and in all medical societies and associations; and Longcope who has carried on the tradition: a teacher, clinician, investigator and author.

And internal medicine has learned much from the scientific studies made on the medical wards of this hospital. It was from here came the classical papers on the visceral manifestations of the erythema group and on polycythemia; the description of the eosinophilia of trichiniasis; the famous monograph on bacterial endocarditis and the more recent studies on the streptococcus and on nephritis, to name only a few.

President Gilman is often credited with having had uncanny skill in selecting that famous first faculty, but it seems that later choices have been just as happy. The American College of Physicians would have been proud to have counted all of these men among its members but it was not founded in time. It has, however, included in its Fellowship not only Dr. Thayer, Dr. Barker and your present Physician-in-Chief, but many of the graduates of this Hospital.

That so many different aspects of Medicine are represented here today is significant of the solidarity of medicine as a whole and of the interdependence of its various divisions. The hospital, the doctor, the nurse, and all those agencies directed to scientific progress and medical education, graduate and undergraduate, together form that whole we call Medicine.

And it is to Medicine in this all inclusive sense that we have each devoted our lives. Some are enlisted in one branch of the service, some in another; some are grouped for one purpose, others for another, but all have joined for the duration of an endless war, striving to reach an unattainable goal. Individually and collectively we love and serve that discipline, system, craft or art called Medicine. To advance Medicine we must give ourselves unselfishly, and we must integrate our organized efforts to this end.

Today we are celebrating not the mere existence of the Johns Hopkins Hospital for the period of fifty years but the remarkable influence of this institution on Medicine during the past half century. This has been an era of amazing medical progress and to this the Johns Hopkins Hospital has greatly contributed and is contributing today.

It is very proper, therefore, that both as individuals and as representatives of groups dedicated to this same end we should congratulate the Johns Hopkins Hospital upon its past achievement, its present vitality and its promise for an even brighter future. In the name of the American College of Physicians it is my privilege to deliver this greeting to the Johns Hopkins Hospital on its fiftieth anniversary.

#### THE NEW ORLEANS SESSION

The Twenty-Third Annual Session of the American College of Physicians, held in New Orleans, was an eminently successful one. All meetings were well attended, including those of the executive boards.

On the evening preceding the opening of the Session, there was a combined dinner of the Board of Regents and the Board of Governors, with members of the Committee on Postgraduate Education, members of the American Board of Internal Medicine, local committee men from New Orleans and the Secretary of the Council on Medical Education and Hospitals of the American Medical Association present. The meeting was devoted to a discussion of graduate and postgraduate medical education, including not only the intensive postgraduate courses which are now being sponsored by the College, but also a discussion of the training and facilities for specialization in internal medicine or one of the allied specialties. The meeting was attended by 22 Officers and Regents, 45 Governors and 15 guests, and the majority of those present engaged in the discussion. At this meeting there was a report on the registration and attendance at the post-graduate courses sponsored by the College during the two-week period just preceding the New Orleans Session, which report herewith follows:

	General Medicine Baltimore	Cardiovascular and Respira- tory Diseases Baltimore	Cardio-Renal- Vascular Medicine Chicago	Cardio- vascular Diseases St. Louis	Diseases of the Glands of In- ternal Secre- tion St. Louis	Total
ALABAMA.....					2	2
CALIFORNIA.....			1			1
COLORADO.....			1			1
CONNECTICUT.....	3					3
DISTRICT OF COLUMBIA.....	5					5
FLORIDA.....	2					2
GEORGIA.....	4					4
IDAHO.....			1			1
ILLINOIS.....		1	1		1	3
IOWA.....				1		1
KANSAS.....					4	4
KENTUCKY.....			1	1	1	3
LOUISIANA.....		1				1
MAINE.....	1					1
MARYLAND.....	2	3				5
MASSACHUSETTS.....	4		1	1		6
MICHIGAN.....	2	1	4	1		8
MISSOURI.....	1					1
MONTANA.....					1	1
NEBRASKA.....	1		1	2		4
NEW JERSEY.....		1				1
NEW YORK.....	7	1	2		1	11
NORTH CAROLINA.....	2		1			3
OHIO.....	2	1	1	1	2	7
OKLAHOMA.....				1	1	2
OREGON.....			1			1
PENNSYLVANIA.....	8	4	2	1		15
TENNESSEE.....	1				1	2
TEXAS.....	1					1
VERMONT.....	1					3
VIRGINIA.....	1	1		1		3
WASHINGTON.....			2	1	1	4
WEST VIRGINIA.....	1			1	1	3
WISCONSIN.....	1		2	1		4
HAWAII.....			1			1
CANADA:						
New Brunswick..		1				1
Ontario.....	1					1
	51	15	23	13	16	118

An analysis of the registration at the New Orleans Session discloses the largest gross registration in the history of the College, 2675; but the net physician attendance ranked in fourth place. There were 578 ladies registered, a number greatly exceeding that of any previous meeting. A comparison of the registration for the past five years follows:

	Mem- bers	Guest Physi- cians	Guest Non- Physi- cians	Stu- dents	Ex- hibi- tors	Ladies	Misc.	Total
New Orleans (1939)	891	524	10	499	167	578	6	2675
New York (1938)	1447	463	24	3	291	319		2547
St. Louis (1937)	877	589	30	414	201	210		2321
Detroit (1936)	733	539		172	132	103		1679
Philadelphia (1935)	923	749		346	231	195		2444

At the New Orleans Session the attendance records show that there were physicians present from forty-seven States of the United States, five Provinces of Canada, the Canal Zone, Hawaii, Puerto Rico, China and Mexico.

The full personnel of new committees, Officers, Regents and Governors appear on the inside cover pages of this issue (May).

At the conclusion of the Session there was a post-convention tour to Mexico City, patronized by a group of twenty-seven, consisting of members of the College and their families. Still a larger group of approximately eighty physicians and their families returned to New York on a post-convention cruise by way of the S. S. Dixie. Both post-convention trips were highly successful and contributed much to the enjoyment and pleasure of those participating.

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#### 1940 SESSION OF THE COLLEGE

Dr. Howard T. Karsner, F.A.C.P., of Western Reserve University School of Medicine, has been appointed General Chairman of the Twenty-Fourth Annual Session of the College, to be held in Cleveland, Ohio, April 1-5, inclusive, 1940.

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#### *Correction*

In the obituary of the late Dr. Carl Boettiger, appearing in the March, 1939, issue of the ANNALS OF INTERNAL MEDICINE, it should have been stated that during the World War Dr. Boettiger was in charge of the Laboratory of the Base Hospital at Camp Bowie, instead of in charge of the Base Hospital.

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#### CENTENNIAL CELEBRATION OF DUKE UNIVERSITY

Upon appointment by ex-President Kerr, Dr. Charles H. Cocke, Governor of the College for the State of North Carolina, was the official delegate of the American College of Physicians to the centennial celebration of Duke University at Durham, April 21-23. The academic procession was notable for its size, there being present approximately 90 per cent of the representatives of the 395 universities, colleges, scientific and literary organizations which had accepted. Addresses were delivered by Dr. John H. Finley, President H. M. Wriston, Dr. Eduard Benes, late President of Czechoslovakia, and by President Dodds of Princeton.

Through the courtesy of its official delegate, the American College of Physicians was presented with a bound autographed copy of "The Architecture of Duke University."

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#### NEW LIFE MEMBER

Dr. Alexander G. Brown, Jr., F.A.C.P., Richmond, Va., became a Life Member of the American College of Physicians on April 10, 1939.

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#### GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

#### *Reprints*

Dr. Thomas W. Baker (Associate), Charlotte, N. C.—7 reprints;  
Dr. Edward G. Billings (Associate), Denver, Colo.—2 reprints;  
Dr. Preston V. Dilts (Associate), Pittsfield, Ill.—1 reprint;

Dr. Alfred Winfield Dubbs (Associate), Allentown, Pa.—1 reprint;  
Dr. Edgar Durbin, F.A.C.P., Denver, Colo.—1 reprint;  
Dr. Norbert Enzer, F. A. C. P., Milwaukee, Wis.—1 reprint;  
Dr. James William Finch (Associate), Hobart, Okla.—1 reprint;  
Dr. A. Allen Goldbloom, F.A.C.P., New York, N. Y.—1 reprint;  
Dr. Jacob Gutman, F.A.C.P., Brooklyn, N. Y.—6th Supplement, Second Series, to  
"Modern Drug Encyclopedia";  
Dr. Howard T. Karsner, F.A.C.P., Cleveland, Ohio—19 reprints;  
Dr. Samuel R. Kaufman (Associate), Wilkes-Barre, Pa.—1 reprint;  
Dr. William H. Kraemer, F.A.C.P., Wilmington, Del.—1 report;  
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—5 reprints;  
Dr. Arthur J. Logie (Associate), Jacksonville, Fla.—2 reprints;  
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—2 reprints;  
Dr. Frank B. Queen (Associate), Chicago, Ill.—1 reprint;  
Dr. Louis H. Sigler (Associate), Brooklyn, N. Y.—1 reprint;  
Dr. H. A. Slesinger (Associate), Windber, Pa.—1 reprint;  
Dr. William H. Walsh, F.A.C.P., Chicago, Ill.—2 reprints;  
Dr. Burton L. Zohman, F.A.C.P., Brooklyn, N. Y.—1 reprint.

Acknowledgment is also made to Dr. J. R. Schramm, Professor of Botany at the University of Pennsylvania, of his gift of a reprint entitled "Cost Analysis of Scholarly Periodical Printing," from the Proceedings of the American Philosophical Society.

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Dr. Edward Bigg (Associate) has accepted an appointment as Instructor in the Department of Medicine of the University of Chicago, beginning July 1, 1939. Dr. Bigg has held a similar position in the Department of Medicine of the University of Michigan.

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Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, has been promoted to Assistant Professor of Medicine in charge of the Department of Cardiology at the Woman's Medical College of Pennsylvania.

Dr. Leaman addressed the West Philadelphia Medical Association January 24, 1939, on "Some Curable Types of Heart Disease"; the Montgomery County Medical Society March 1 on "Prognosis in Heart Disease"; the New Castle County Medical Society at Wilmington, Del., March 21, on "Heart Block and the Adams-Stokes Syndrome"; the Atlantic County Medical Society, April 14, on "Modern Trends in the Treatment of Cardiovascular Disease"; the American Association of the History of Medicine at its fifteenth annual meeting, Atlantic City, May 1, on "Medical History in Clinical Teaching."

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Dr. L. Minor Blackford, F.A.C.P., Atlanta, Ga., was recently promoted from Instructor to Associate in Medicine at Emory University School of Medicine, Associate Visiting Physician at Emory University Hospital and Assistant Physician in the Emory University Division of Grady Hospital.

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Recent announcement was made by President Winfred G. Leutner of Western Reserve University, Cleveland, of a grant of \$4,100 to Dr. Carl J. Wiggers, F.A.C.P., Professor of Physiology of the School of Medicine, from the John and Mary Markel Foundation, of which J. Pierpont Morgan is President, whose object is "to support research programs in medical science." This grant is for a study of the nature of ventricular fibrillation by means of desensitizing the heart.

Dr. Edward Strecker, F.A.C.P., Philadelphia, delivered a Salmon Lecture before the New York Academy of Medicine on April 14, 21 and 28, and before the University of Toronto on May 5, his subject being "Beyond the Clinical Frontiers." Salmon established a fund of \$100,000 in the field of psychiatry and the lectureship has been assigned for approximately seven years. The lecturer receives the income from the fund, amounting to about \$2,500. He must deliver a series of lectures and present the manuscript for a book.

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Dr. Frank S. Horvath, F.A.C.P., Washington, D. C., was appointed Medical Director of the Outpatient Department of Georgetown University Hospital and Director of Student Instruction in the same department on March 1.

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Dr. Samuel M. Feinberg, F.A.C.P., Chicago, addressed the Michigan Allergy Society at Ann Arbor on March 16 on "Mold Allergy." He also addressed the Boone-Story County (Iowa) Medical Society on March 22 on "The Rôle of the General Practitioner in Allergy."

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Dr. H. I. Spector, F.A.C.P., St. Louis, was the guest of the Sedgwick County Medical Society, Wichita, Kan., at their Third Spring Clinical Assembly on March 21, 1939. In the morning he spoke on the subject of "Treatment of Pulmonary Tuberculosis with Special Emphasis on Collapse Therapy." At the noon meeting he conducted a round-table discussion and in the evening he spoke on the subject of "Differential Diagnosis of Hemoptysis."

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Under the presidency of Dr. Samuel E. Munson, F.A.C.P., College Governor for Southern Illinois, the Illinois State Medical Society held its 99th annual meeting at Rockford, Ill., May 2, 3, and 4, 1939. Dr. Munson's presidential address was entitled, "Shall Organized and Scientific Medicine Continue Its Progress."

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The Alameda County Tuberculosis and Health Association conducted a panel discussion and demonstration of tuberculosis prevention and treatment at Oakland, Calif., on April 19. Among those appearing on the panel were Dr. B. W. Black, F.A.C.P., Medical Director of Alameda County; Dr. Harold G. Trimble, F.A.C.P., Chief of the Tuberculosis Service, Alameda County Institutions; and Dr. Chesley Bush, F.A.C.P., Superintendent of Arroyo Del Valle. The panel discussion included the presentation of patients, methods and technics of treatment and prevention.

## RECENT ANNOUNCEMENTS

The University of Wisconsin Medical School is to conduct an Institute for the Consideration of the Blood and Blood-Forming Organs, September 4-6, 1939. The program is to include papers and round-table discussions by European and American workers in the field of hematology. In addition to the discussions, the following formal papers are to be presented:

- Dr. L. J. Witts, Oxford, England, Anemias Due to Iron Deficiency.  
Dr. Cecil J. Watson, Minneapolis, The Porphyrins and Diseases of the Blood.  
Dr. Cornelius P. Rhoads, New York, Aplastic Anemia.  
Dr. E. Meulengracht, Copenhagen, Denmark, Some Etiological Factors in Pernicious Anemia and Related Macrocytic Anemias.  
Dr. Harry Eagle, Baltimore, The Coagulation of Blood.  
Dr. George R. Minot, Boston, Anemias of Nutritional Deficiency.  
Dr. Russell L. Haden, Cleveland, The Nature of the Hemolytic Anemias.  
Dr. Jacob Furth, New York, Experimental Leukemia.  
Dr. Claude E. Forkner, New York, Monocytic Leukemia and Aleukocythemias.  
Dr. Edward B. Krumbhaar, Philadelphia, Hodgkin's Disease.  
Dr. Louis K. Diamond, Boston, The Erythroblastic Anemias.  
Dr. Edwin E. Osgood, Portland, Marrow Cultures.  
Dr. Charles H. Doan, Columbus, The Reticulo-Endothelial System.  
Prof. Hal Downey, Minneapolis, Infectious Mononucleosis.  
Dr. Paul Reznikoff, New York, Polycythemia.

Physicians and others who are interested are cordially invited. A detailed program may be obtained by addressing Dr. Ovid O. Meyer, Chairman of Program Committee, University of Wisconsin Medical School, Madison, Wisconsin.

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The Twelfth Graduate Fortnight of The New York Academy of Medicine will be held from October 23 to November 3, 1939.

The subject of this year's Fortnight is THE ENDOCRINE GLANDS AND THEIR DISORDERS.

The Fortnight will present a carefully integrated program which will include clinics and clinical demonstrations at many of the hospitals of New York City, evening addresses, and appropriate exhibits. The evening sessions at the Academy will be addressed by recognized authorities in their special fields, drawn from leading medical centers of the United States. The comprehensive exhibit will include books and roentgenographs; pathological and research material; and clinical and laboratory diagnostic and therapeutic methods. It is also planned to provide demonstrations of exhibits. All members of the medical profession are eligible for registration.

A complete program and registration blank may be secured by addressing Dr. Mahlon Ashford, The New York Academy of Medicine, 2 East 103 Street, New York City.

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Vanderbilt University Medical School has announced a graduate course in Internal Medicine designed for those desiring special training in this field.

The course will extend over a period of one year and will be open to physicians who have completed an internship, have had an additional year's experience as assistant resident in medicine or its equivalent and are acceptable to the school. The first course will begin July 1, 1939, and is limited to six students. Tuition fee—\$300.

Three fellowships are available for the course. These fellowships, which provide tuition, board, and lodging, are open to those who meet the requirements mentioned above and will be awarded on the basis of the individual's training and recommendations.

Applications for the course and the fellowships will be received by the Director of Postgraduate Instruction, Vanderbilt University Medical School, from whom further information regarding the course and the fellowships can be obtained.

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The cardiovascular department of the Michael Reese Hospital (29th and Ellis Ave., Chicago, Illinois) offers a full-time intensive course in Electrocardiography (August 21–September 2, 1939) by Dr. Louis N. Katz, Director of Cardiovascular Research.

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The Fourth Annual Convention of the National Gastroenterological Association will be held on June 1 and 2, 1939, at Squibb Hall, Squibb Building, 745 Fifth Avenue, New York, N. Y. A very interesting program is assured.

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The American Congress on Obstetrics and Gynecology, which will meet in Cleveland (September 11–15, 1939), has a section on Medicine and a section on Public Health. The preliminary programs of these two sections have been issued and contain many papers which are of interest to all internists. Registration fee to the Congress will be \$5.00. Applications may be addressed to The American Congress on Obstetrics and Gynecology, The Annex, 650 Rush Street, Chicago, Illinois.

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The Society for Investigative Dermatology and the Journal of Investigative Dermatology were recently inaugurated. This Society and its Journal are serving to bring together scientific investigators who are particularly interested in studies in dermatology and venereology and in using the skin as a test tissue for the study of fundamental problems. Membership is open to any physician in good standing or one engaged in teaching or in scientific research in medicine or allied subjects in a reputable university, college, laboratory, hospital or other institution. The secretary is Dr. S. W. Becker, School of Medicine, University of Chicago, Chicago, Illinois.

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Announcement has been made of a new scientific periodical entitled "Psychosomatic Medicine" to be published quarterly (January, April, July and October) with the sponsorship of The Committee on Problems of Neurotic Behavior, Division of Anthropology and Psychology—National Research Council. Each number is to consist of approximately 125 pages totaling between 500 and 600 pages per volume. An Editorial Board, all specialists in their fields, has been organized to reach prompt decision upon all contributions submitted.

The aim of Psychosomatic Medicine is to encourage and bring together studies which make a contribution to the understanding of the organism as a whole, in somatic and psychic aspects. These materials are now usually separated widely in manner and place of publication because of differences in concept, approach and methods. The sponsoring groups feel that this constitutes an urgent practical need for a new channel of scientific interchange. This journal will provide both an integrating medium and a means of prompt and inexpensive publication.

Subscriptions to Psychosomatic Medicine for one year will be \$5.00; for two years, \$9.00 (outside U. S. and Canada: for one year, \$5.50; for two years, \$10.00); single copies, \$1.75. They should be addressed to Dr. Flanders Dunbar, Managing Editor, 2 East 103rd Street, Room 445, New York, N. Y.

For the past three years the RADIOLOGIC REVIEW AND MISSISSIPPI VALLEY MEDICAL JOURNAL has served as the official publication of the Mississippi Valley Medical Society and has devoted most of its pages to this purpose. With the continued growth of that society it has seemed fitting that the name of its official publication more clearly indicate its principal function, hence the new name—"MISSISSIPPI VALLEY MEDICAL JOURNAL (Incorporating the RADIOLOGIC REVIEW)." Like its predecessor, the new publication will be a bimonthly and essentially clinical, especially appealing to the general practitioner. Subscriptions should be addressed to Dr. Harold Swanberg, Editor, Mississippi Valley Medical Journal, P. O. Drawer 110, Quincy, Illinois.

The Medical Faculty of the University of Paris, in collaboration with the Association pour le Développement des Relations Médicales and the American Medical Society of Paris, has organized courses in English for graduates in medicine. The cost of a course is generally six dollars per lesson, whether taken privately or by a group, and is divided between the students.

The Faculty of Medicine will grant, for post-graduate work done here, a certificate, to physicians who are graduates of a reputable medical college and who have taken courses during a period of no less than two months in Paris. Those certificates will bear the Dean's signature.

For all inquiries, apply to the office of the Association pour le Développement des Relations Médicales (A.D.R.M.), Salle Bécларd, Faculté de Médecine, 12, rue de l'Ecole-de-Médecine, Paris.

The Istituto Di Malariologia at Rome offers international courses in malariology this year from July 25 to September 20. These courses will include instruction in the laboratory aspects of malarial disease, in the pathology and clinical aspects of malaria, in malarial entomology, epidemiology and prophylaxis. In addition to lectures and demonstrations there will be practical work in the laboratory and wards, residence in experimental stations, and excursions to malarial regions in Italy.

The course is open exclusively to postgraduate physicians. It is stated that it will be held in French if required and if 10 students are attending. In any case, one or more interpreters will be available. Tuition fee, including obligatory trips, is 400 Lire. Applications must be received before June 20, 1939, and should be addressed to The Director, G. Bastianelli, Istituto Di Malariologia "Ettore Marchiafava," Rome, Italy.

The German authorities for postgraduate medical instruction have arranged a number of international courses for specialists for the summer of 1939.

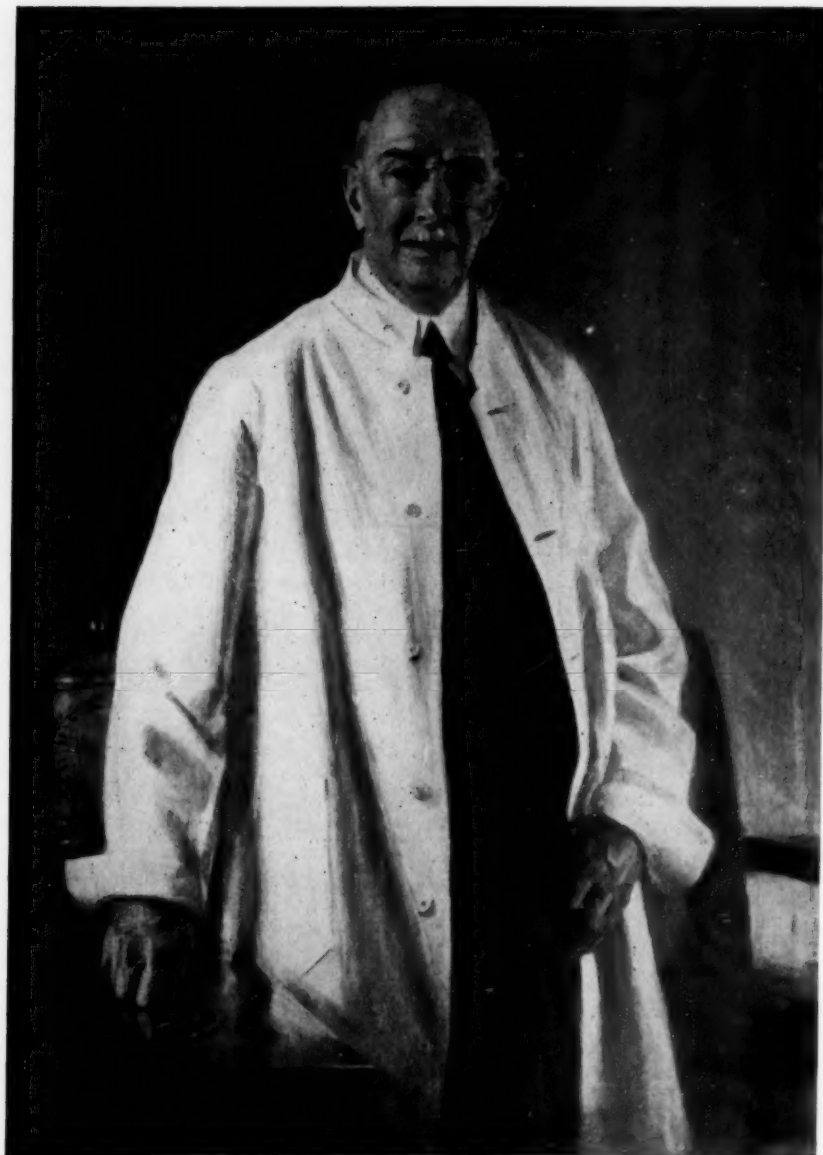
All courses will be held in the German language. The number of participants is limited.

Information and prospectuses through:

Ärztliches Fortbildungswesen, Berlin N. W. 7., Robert-Kochplatz 7, Kaiserin-Friedrich-Haus.

The Seventh Congress of Biologic Chemistry will meet in Liège, Belgium, from October 13-15, 1939.

The National Library of Peiping (Kunming, China) states that, in order to keep Chinese scholars informed as to the recent development of various branches of science, the Library is building up a special Reprint Collection which will be of great value to investigators engaged in scientific research. They are in urgent need of books and periodicals of all kinds, old or new, especially standard works in various fields. Donations of reprints and books from American and Canadian authors may be sent care of the International Exchange Service, Smithsonian Institute, Washington, D. C., which makes monthly shipment to China.



DR. ALFRED STENGEL  
MASTER OF THE AMERICAN COLLEGE OF PHYSICIANS

## OBITUARIES

## DR. ALFRED STENGEL

## AN APPRECIATION

There are some who possess that intangible quality known as leadership, to whom all others turn for counsel, guidance and inspiration. Such a man was Alfred Stengel whose sudden and unexpected death on April 10, 1939 deprived American Medicine of one of its most distinguished clinicians and robbed the American College of Physicians of a beloved and honored Master as well as a loyal and ardent champion.

Dr. Stengel was born in Pittsburgh, Pa. on November 3, 1868. He received his medical degree from the University of Pennsylvania in 1889, after attending the Biological Department of the University of Pennsylvania. In the early part of his career he devoted himself enthusiastically to pathology, thereby laying a firm foundation for the years of achievement in clinical medicine that were to follow. He not only served as Pathologist to the Lankenau Hospital and as one of the pathologists at the Philadelphia General Hospital, but also published a justly popular and widely used Textbook of Pathology. His career as a clinical teacher began with his appointment as Instructor in Clinical Medicine at his Alma Mater in 1893. By the age of 30, he was made Clinical Professor of Medicine, a post which he held until he became Professor of Medicine at the University of Pennsylvania in 1911. It was during these years that he gained his well deserved popularity with students and physicians alike as an astute clinician and a scholarly, brilliant teacher whose clinical lectures were masterpieces of concise expression and clear thinking. From the time of his appointment, until his retirement as Professor of Medicine in 1936, he showed a keen interest in and a profound understanding of the problems of medical education, re-organizing the Department of Medicine at the University of Pennsylvania and introducing many far reaching and important changes. As a result of his versatility and ability, he was the first appointee as Vice President in Charge of Medical Affairs of the University of Pennsylvania. With characteristic unselfishness, he assumed this difficult position in 1931. In this post he had unusual opportunities to demonstrate his exceptional ability as an administrator. Dr. Stengel accomplished the arduous and important task of coördinating all the various medical activities and allied departments of the University of Pennsylvania and the present efficient organization is a tribute to his foresight and genius.

During his years of active medical practice and teaching, he served as Physician to a number of the leading hospitals of Philadelphia, including the Pennsylvania Hospital, the Hospital of the University of Pennsylvania and the Philadelphia General Hospital. In recognition of his great contributions to medical science and to medical education in this country, he was accorded the honorary degrees of LL.D. from the University of Pennsylvania, Sc.D. from the University of Pittsburgh and LL.D. from Lafayette College.

Not long after his graduation, he became associated with that outstanding figure in American Medicine, the late Provost of the University of Pennsylvania, Dr. William Pepper, who early recognized in the young Alfred Stengel, a man destined to take a conspicuous place in the medical activities, not only of Philadelphia, but of the nation. This close association with the brilliant Pepper had a profound effect upon the development of the alert, energetic and keen minded Stengel.

Dr. Stengel made numerous outstanding contributions to the leading medical works of his time, among the most important of which were: Diseases of the Blood to Twentieth Century Practice, Diseases of the Intestines in Osler's Modern Medicine, Diseases of the Liver in Nelson's Loose Leaf System of Medicine, in addition to many others of equal importance. For a number of years he edited the American Journal of Medical Sciences. One of the literary achievements of which he was most proud was his editorship of the English edition of Nothnagel's System of Medicine.

The eagerness with which Dr. Stengel's advice was sought by various groups is well illustrated by his membership on the following boards: Board of Managers of the University Hospital, of the Wistar Institute of Anatomy, of which Board he later became President, of the Graduate Hospital of the University of Pennsylvania and the Pepper Clinical Laboratory of which he became the Director, as well as the Board of Trustees of the University of Pennsylvania. In these capacities, he was able to exercise a far reaching influence in the conduct of the affairs of the University of Pennsylvania. He was a member of many important national medical societies including the Association of American Physicians and that venerable organization, The American Philosophical Society. One of the greatest honors that came to him was that of being President for three successive terms of that august body, The College of Physicians of Philadelphia.

His activities and accomplishments in the field of medicine and the medical sciences, as well as his influence upon the City of Philadelphia and his Alma Mater, might be dwelt upon at great length, but the interest of the American College of Physicians in Dr. Stengel is not based primarily upon the fact that he was an outstanding clinician, a brilliant teacher and an able administrator, but rather upon his never failing interest in and contributions to our organization.

In 1923 he became a Fellow of this College. About this time, it became apparent that, if the College was to attain the high purposes for which it was organized, changes must be brought about in its administration. To Dr. Stengel, it was obvious that a critical point in the history of the College had been reached. With characteristic energy and wisdom, he applied himself to the task of saving the College by bringing about a much needed reorganization. The eminent position and the influence which the College exercises today in American Medicine are largely the result of Dr. Stengel's foresight and determination. It is not surprising, therefore, that in 1925 he became

the Fourth President of the College and, in spite of the great press of other work, consented to serve as President a second term in order to complete the extensive changes that he had instigated. In 1926 he became the first Life Member of the College. In recognition of his outstanding service to the College and his preëminent position in medicine, he became its Second Master in 1929. From the time that he retired from the Presidency to the day of his death, Dr. Stengel served continuously on the Board of Regents or on some committee of the College. In 1935 he was the General Chairman of the Annual Clinical Session that was held in Philadelphia. From the time when he first became a Fellow, Dr. Stengel evinced untiring interest in the affairs of the American College of Physicians. It may be said, without fear of contradiction, that he laid the foundation for the high academic standards and sound economic policies that are today characteristic of the College and, through his example and inspiration, he did much to bring the College to the point where it exercises an important national influence in Internal Medicine.

Dr. Stengel's loss will be keenly felt throughout the College but especially by those who have had the privilege of being closely associated with him during his years of activity in this organization.

GEORGE MORRIS PIERSOL, M.D., F.A.C.P.,  
Secretary General, American College of Physicians.

#### DR. AMOS HENRY STEVENS

Dr. Amos Henry Stevens, prominent Fairmont, West Virginia, internist, and for ten years Secretary of the Marion County Medical Society, died suddenly at his home on March 11, 1939, following a heart attack. He was 40 years of age.

Dr. Stevens was born in Portland, Maine, on July 23, 1899. Following his early education there, he attended the Massachusetts Institute of Technology, graduating in 1922. He received a Certificate of Public Health from the same institution in 1923. In 1926 he received his M.D. degree from Harvard University. Then followed two years internship at the Henry Ford Hospital.

Dr. Stevens located in Fairmont early in 1929 and served for one year as Chief of the Fairmont City Hospital Medical Staff. The same year he was elected Secretary of the Marion County Medical Society, a position he held until shortly before his death. In addition to his many other medical organization activities, he was a member of the Syphilis Committee of the West Virginia State Medical Association and was particularly interested in syphilis control work.

Dr. Stevens, as well as being affiliated with county, state, and national associations, was a Fellow of the American College of Physicians, a Diplomate of the American Board of Internal Medicine, and a 1927 Diplomate

of the National Board of Medical Examiners. His practice was limited to internal medicine and he was recognized by his associates as one of the outstanding internists of Northern West Virginia.

Funeral services were held on March 14, and interment was made in the family burial ground, Arlington, Massachusetts. Dr. Stevens is survived by his wife, Julia Stevens, former President of the Womans Auxiliary to the State Association, and three sons.

ALBERT H. HOGE, M.D., F.A.C.P.

Governor for West Virginia.